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Questionnaire survey

In 1998 Dr Simon Cathcart of the Wellcome Trust attended the 15th International Leprosy Conference in Beijing to promote the Topics in International Health (TIH) Leprosy CD-ROM. Following its successful launch at this prestigious conference, the TIH Leprosy disk now has some 400 users worldwide. In 1999 the TIH series as a whole was awarded a commendation by the British Medical Association in their annual medical book competition (electronic media) and to date more than 5000 disks in the series are being used in 89 countries, with the numbers growing steadily each month.

This year, the Trust has collaborated with Netherlands Leprosy Relief (NLR) to produce two translations of the leprosy disk, one into Portuguese and the other into Bahasa Indonesia. NLR will distribute the translated disks directly to their networks of local healthcare workers. This is the first translation of any of the TIH disks into a foreign language and will serve to increase usability in three countries with the highest endemicity of leprosy worldwide: Brazil, Mozambique and Indonesia.

As part of their continued programme of evaluation and improvement of the TIH series the Wellcome Trust, in collaboration with Leprosy Review, now invites individuals who have used the Leprosy CD-ROM to submit their overall impressions of this training tool, e.g. design, functionality, ease of use, etc. In addition, we would like to find out how useful the tutorials and images are in enabling individuals to recognise when a person has leprosy.

A questionnaire survey can be accessed and submitted through the LEPRA website (http://www.lepra.org.uk) or by e-mail, fax or post (details below). All responses will be treated with the strictest confidence and data gathered from the forms will be anonymous. However, it would be helpful if you could tell us where you used the disk (country and type of institution) and at what level you normally work (student, primary health care, nurse, doctor etc.).

The questionnaire should not take you more than 10 minutes to complete and all individuals who submit a completed questionnaire (by whatever means) before 1st September 2000 will be entered into a prize draw. The first three names selected at random on 1st September will receive a CD of their choice from any of the currently available TIH titles.

We look forward to reading your responses and wish you all the very best of luck in the prize draw. Thank you for your help and co-operation.

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LEPRA web site address: http://www.lepra.org.uk
Details of the TIH series and how to order are available by contacting: CAB International, Wallingford, Oxon, OX10 8DE, UK. Phone: 44 (0)1491 832111; Fax: 44 (0)1491 829292; e-mail: publishing@cabi.org

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Editor's Choice

This issue is bulging with interesting articles, so sit tight for a good read. The first article from the Girdhar team in Agra, India (p 144) reports on relapse rates in multibacillary patients treated with MDT either to smear negativity or for a fixed duration. Although this is not a randomized controlled trial, it has valuable data. The key finding is that if a patient has a BI ≥ 4 at the start of treatment, they are four time more likely to relapse when treated with fixed duration therapy rather than until smear negativity. I'm sure this paper will provoke considerable discussion, since it has implications for patients, clinicians and planners. It again highlights the importance of identifying patients with a high bacterial load at the start of treatment. With the abandonment of smear taking this is going to be difficult to achieve.

There is more interesting data from the Bangladesh group who have reported (p 154) on the outcome of patients who had acute nerve function impairment. One-third of nerves did not improve and 12% deteriorated despite steroid treatment. This again highlights the need for developing new treatment beyond steroids for acute nerve damage. The authors also very honestly report on the 30% of patients in their study who should have received steroid treatment but did not. Of these patients, 62% had spontaneous recovery of sensory function but only 33% had spontaneous recovery of motor function. This is a fascinating finding and should make us aware that improvements we ascribe to steroid treatment may occur anyway. It should also raise awareness that the risk/benefit ratio for treating patients with steroids may be weighted more towards risk than has previously been recognized.

Sensory testing is revisited. David Warndorff has contributed a useful description of how to do sensory testing properly in Your Questions Answered (p 219). The effect of age in sensory testing has not previously been considered. Age not only wearies, it also makes your feet less sensitive; Mitchell and Mitchell (p 169) have shown that the threshold for sensory testing in the foot increases with age. So don't be too keen to ascribe foot anaesthesia to leprosy in elderly patients.

It is a pleasure to have another review on women and leprosy. This was the other award-winning essay in last year's Lepra essay competition for medical students and looks at the problem for women with leprosy from a social and anthropological perspective. After this article you may like to turn to the article on scholarship projects in Turkey. This is heartening for it shows that female children of leprosy patients have particularly benefited from opportunities to extend their education.

We also have two papers on the trials of *Mycobacterium w* vaccine. These report in considerable detail the impact of the vaccine. Whilst the vaccine clearly speeds bacteriological clearance, there is a price to pay for this. Again, patients with an initial high BI are at significantly increased risk of having type 1 reactions and this has to balanced against the benefit of bacterial clearance.

Many people will have seen the Wellcome Trust CD-ROMs on leprosy and other tropical diseases. It is important that these new teaching materials should be evaluated and I hope that as many people as possible will apply for and complete the questionnaire about the CD-ROM.

DIANA N. J. LOCKWOOD

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REVIEWS

The value of DALY life: problems with ethics and validity of disability adjusted life years

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Disability adjusted life years (DALYs) have been launched by the World Bank and backed by the World Health Organisation as a measure of the global burden of disease.[1,2] The aim is ambitious: 'The burden of disease has yet to entirely replace traditional approaches to the assessment of health needs as an influence on political decision making.'[3]

Just like quality adjusted life years (QALYs), DALYs combine information about morbidity and mortality in numbers of health years lost. In the DALY approach, each state of health is assigned a disability weighting on a scale from zero (perfect health) to one (death) by an expert panel.[2] To calculate the burden of a certain disease, the disability weighting is multiplied by the number of years lived in that health state and is added to the number of years lost due to that disease (Figure 1). Future burdens are discounted at a rate of 3% per year, and the value of the lifetime is weighted so that years of life in childhood and old age are counted less.

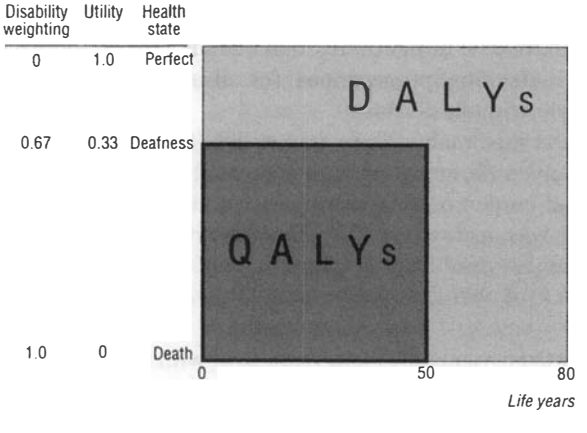

Figure 1. DALYs and QALYs are complementary concepts. QALYs are years of healthy life lived; DALYs are years of healthy life lost. Both approaches multiply the number of years (x axis) by the quality of those years (y axis). QALYs use 'utility' weights of health states; DALYs use 'disability weights' to reflect the burden of the same states. For example, if the utility of deafness is 0.67, the disability weight of deafness is $1-0.67=0.33$. Disregarding age weighting and discounting, and assuming life expectancy of 80 years, a deaf man living 55 years represents $0.67\times 50=33.4$ QALYs gained and 0.33×50. $30\times 1=46.6$ DALYs lost.

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Summary points

DALYS (disability adjusted life years) have been launched by the World Bank and the World Health Organisation as a combined measure of morbidity and mortality

The DALY approach explicitly presupposes that the lives of disabled people have less value than those of people without disabilities

The method assumes that disabled people are less entitled to scarce health resources for interventions that would extend their lives

These assumptions are in contrast with basic principles of the WHO

Forced consistency between questions that address different issues produces disability weightings that are basically artefacts, this affects the validity of the global burden of disease report

The ongoing revision of the DALY protocol should address these problems

Though the idea of expressing burden of disease in a single index is tempting, any attempt to summarise information about quality of life and length of life in one number is bound to run into conceptual and methodological problems. The DALY review group of the WHO has criticised DALYs for obscuring too much by pressing complex information into a single numeric measure with a mathematical formulation that 'only serves to distract attention from the main issues.' Others have raised objections to the way in which DALYs are currently calculated.[4–7] Among these objections are that discounting future health gains and losses is disadvantageous for preventive medicine, children, and future generations; that age weighting disfavours children and old people, that the chosen estimates for life expectancy tend to disfavour women; that the expert panels reflect the values of a skewed sample of the population; that age weighting and discounting measures the social usefulness of people's life years rather than the individual utility of life; and that the DALY approach implicitly attaches lower value to life extending programmes for disabled people than to corresponding programmes for people without disability.

Our paper considers this final point in greater detail. After Anand and Hanson noted this problem,[5] a completely different procedure for weighting disabilities was adopted in the protocol for the global burden of disease project.[2] In the new procedure, the devaluation of life in disabled people was made explicit. An international research group that intended to use the procedure to establish disability weightings for Europe recently became aware of the offensiveness and lack of validity of the method (see below) and is now finding a new valuation method.[8]

The WHO has started revising the DALY protocol with a view to launching a new version in 2003. This paper aims to draw wider attention to the problems of the existing valuation protocol, in the hope that they be dealt with appropriately when the protocol is revised.

The valuation procedure of the DALY approach

Valuing health states numerically on a scale of zero to one is the most problematic part of any measure combining quality and quantity of life. The method used in the global burden of

PTO1—the first person trade-off question

You are a decision maker who has enough money to buy only one of two mutually exclusive health interventions. If you purchase intervention A, you will extend the life of 1000 healthy (non-disabled) individuals for exactly one year, at which point they will all die. If you do not purchase intervention A, they will all die today. The alternative use of your scarce resources is intervention B, with which you can extend the life of *n* individuals with a particular disabling condition for one year. If you do not buy intervention B they will all die today; if you do purchase intervention B, they will die at the end of exactly one year.

disease project is a specific version of the person trade-off technique,[9] which was originally developed to include concerns in the process of valuation.[10,11]

In the DALY protocol, expert panels are asked two different person trade-off questions, and consistency between the two answers is then forced. In the first question (PTO1) panellists are asked to compare the value of extended life in people without disabilities with that in disabled people. It is presumed that lifetime of disabled people is worth less than that of people without disabilities and that disabled people have fewer claims on health resources than do people without disabilities. The task is to find out how much less. This is done by means of the question shown in the box.[9]

Deriving a disability weight from PTO1 is described in the summary of the global burden of disease report:[12] 'if the participant judges that 1000 healthy people would have an equal claim on the resources as 8000 people with some severe disability, the weight assigned to that particular disability is equal to 1 minus 1000 divided by 8000, or 0.875.'

In the second person trade-off question (PTO2) subjects are asked to value cures for different chronic conditions relative to interventions that extend life. For instance, how many people cured of blindness does the respondent consider equal to prolonging the lives of 1000 people? If the response is 5000, the corresponding disability weight of blindness is $1000:5000 = 0.2$. This question raises the kind of issue that may occur in 'real world' priority setting. Unlike the first question, the second does not presuppose that the lifetime of disabled people is devalued.

The validity of forced consistency

At this point it might be argued that there is nothing wrong with asking the first question. If people do not want to discriminate between non-disabled and disabled people in matters of life extension, they may simple answer that $n = 1000$. Unfortunately, this is not possible since consistency with the other question is forced. To see how this works, consider the case of blindness. Assume that a panellist, on ethical grounds, responds that extending the life of 1000 sighted people and 1000 blind people is equivalent. The resulting disability weighting for blindness is zero. Assume that in the second question the panellist answers that relieving 5000 people of blindness is as valuable as prolonging the lives of 1000 people. This gives a disability weighting of 0.2. The valuation so far has yielded two different disability weightings for the same health state. The panellist is now asked to reconsider these responses and choose a new pair of answers to produce the same disability weighting. The panellist might end up by selecting $PTO1 = 1100$ and $PT02 = 11,000$, which together yield a disability weighting of 0.09. This weighting, however, does not correspond to any actual

preference of the respondent: it is basically an artefact, generated by the requirement for consistency between questions that address different issues.

The disability weightings in use[9] tell us that the value of one year for 1000 people without disabilities on average is set equivalent to the value of one year for 9524 people with quadriplegia, 4202 people with dementia, 2660 blind people, 1686 people with Down's syndrome without cardiac malformation, 1499 deaf people, 1236 infertile people, and 1025 underweight or overweight people (2 SD from mean weight : height ratio).

Experience of the method

In May 1998 we participated in a workshop of European researchers working with DALYs. Training sessions to determine the disability weightings of selected illnesses were part of the programme. The sessions followed the global burden of disease protocol, with some adjustments. In PTO1, the response that extended life for 1000 disabled people is as valuable as extended life for 1000 people without disabilities was regarded as unreasonable. Anyone who chose this option was told that he or she was implying that being disabled is as good as being non-disabled and that there is no need to spend resources on disabled people. It was suggested that he or she should therefore indicate a number higher than 1000.

After the meeting, we sent this summary of our perception of the valuation sessions to the other 11 participants, together with some questions. Eight responded: four agreed with the summary completely, three agreed with most of it, and one disagreed. Seven of the eight said that they thought that the two questions ask about different things and that it should be accepted that they produce different disability weightings. Four subjects felt that they were led 'to some extent' to answer in a particular way, and two subjects felt they were led 'to a great extent'.

In spite of their reported view that the two questions ask about different things, participants at the workshop eventually accepted the requirement of consistency. Some explained that they felt they were participating in a game of little practical consequence. Others reported that rather than making person trade-off judgments, they picked disability weightings that 'looked reasonable' and then selected corresponding person trade-off numbers. Perhaps some also accepted the authority of the facilitators and assumed that they were right in what they were demanding, or tried to avoid unpleasantness.

Confusing value of life with health?

The line of thought from the first question to the application in cost effectiveness analysis seems to be that the healthier the person, the more valuable their life is to themself and to society and the greater their claim on restricted healthcare resources to have their life extended. This makes sense only if the value of life is not seen as a dimension distinct from health, but rather as a direct positive function of health. In valuing life as a function of health status, the DALY approach is not alone: QALYs have been criticised on the same grounds,[13–18] and often in history people have been classified and dealt with according to their functional capacity.

A valuation of human beings according to their functional capacity is in sharp contrast to the humanistic values laid down in the Declaration of Human Rights: 'recognition of the

inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation.'[19] The WHO department responsible for the global burden of disease project aims at 'strengthening the scientific and ethical foundations of health policies... The aim of the work is to promote equity, quality, and efficiency.'[20] The current DALY protocol does not seem to accord with this.

Conclusion

The DALY approach currently in use presupposes that life years of disabled people are worth less than life years of people without disabilities. Through the imposition of consistency between substantially different questions, people participating in evaluation panels are forced to adopt discriminatory positions on the value of life of disabled people. In as much as the disability weightings do not correspond to a clear preference but are the results of forced compromise, they must be seen basically as artefacts. Revision of the DALY protocol should deal with these problems appropriately. In particular, the use of disability weightings in the valuation of gained life years should be abandoned.

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A woman with leprosy is in double jeopardy

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Summary The *double jeopardy* associated with female leprosy patients is the central theme underpinning this essay. It constitutes a combination of biological factors unique to women and culturally defined bias, resulting in more stigmatization and isolation for women. Having examined the female immunological response and biological roles, the essay continues by focusing on the gender-culture perspective of leprosy. It draws upon an historical analysis of the experiences of Indian and African women to illustrate the ways in which gender roles impact upon health education and the utilization of health care services. Concluding comments suggest strategies that might improve female leprosy patient status, and views towards future research.

Introduction

Leprosy is one of the oldest diseases known to humankind, and for centuries people with the disease have been stigmatized. Social attitudes, both past and present, exude fear. In developed countries, leprosy is little known yet conjures up visions of deformed, fingerless beggars sitting in busy market squares or street corners in the slums of India or Africa. It is this stereotypical Western view of leprosy that emphasizes the stigma inflicted upon people with leprosy. The purpose of this essay is to examine the additional gender specific social impacts of leprosy on women. This is defined here as the 'double jeopardy'. Specifically, this definition goes further than describing leprosy stigma in general, to include both uniquely female immunological and biological involvement, and the cultural impact on the social status of women that results in the gender bias of health beliefs, attitudes and behaviours. With special reference to the link between gender and culture, the essay will analyse the emerging roles of women in Indian and African culture to provide the background for understanding the specific problems of female leprosy patients in these two broad geographical areas. In the concluding sections, a direction for health prevention and promotion that takes account of the cultural norms and boundaries of women in Africa and India will be sought. This will recognize key challenges in conducting comparative analyses that recognize

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the implications of eurocentric bias. The concluding analysis will, therefore, attempt to synthesize the discussion, as far as is possible, from the cultural perspectives of those studied.

Leprosy and pregnancy

Older hospital-bound data suggested that often appeared first in pregnancy, with reactivation and relapse of pre-existing disease.[1] These observations do not seem to hold true now, but there are no published hard data from leprosy field programmes about pregnancy and first presentation of leprosy. Women are at particular risk of developing type 1 (reversal) reactions during the post-partum period.[2] This puts women at particular risk of developing neuritis and nerve damage.

A major concern for women is the effect that leprosy may have on their children. Pregnancy in mothers with lepromatous leprosy is no more affected by the major complications of pregnancy than other forms.[3] However, neonates appear to weigh less than average, and have a higher incidence of fetal distress and respiratory problems.[3] This has been associated with impaired placental function, detected clinically as intrauterine growth retardation.[4] These babies have a higher incidence of neonatal and infant morbidity due to an increased susceptibility to common childhood infections, and a higher incidence of neonatal death due to respiratory problems. However, these studies relate to mothers treated in the pre-MDT era and data relating to the subcore of pregnancy after MDT treatment are sadly lacking.

The possibility that leprosy is transmitted from mothers to babies *in utero* has been investigated; again, most of the data predate effective combination antibiotic therapy. It was discovered that cord blood IgA was significantly increased in babies of mothers with leprosy, and IgA anti-*M. leprae* antibodies were found in tie cord sera of 30% of these babies.[5] Furthermore, evidence of active production of specific IgA and IgM anti-*M. leprae* antibody was found during the first 6 months of life.[6] This evidence suggests that *M. leprae* crosses the placenta to set up an immune response in the child. However, the incidence of leprosy in children under 2 years of age, born to mothers with active lepromatous leprosy, was only 5%.[7] These babies are at particularly high risk of infection by droplet spread because they are in close contact with mothers who have leprosy, and often share the same under-privileged social circumstances, for example, poor housing, lack of ventilation, and overcrowding. In summary, women are not only disadvantaged by the detrimental effect of pregnancy on leprosy, but also the marked disadvantages that leprosy inflicts on pregnancy and child health. The cultural impact on these biological mechanisms is discussed later.

Cultural and social factors

The double jeopardy of leprosy constitutes not only the integration of the disease with uniquely female immunological and biological influences, but also, and perhaps more importantly, the cultural impact on the social status of women that results in the gender bias of health beliefs, attitudes and behaviours. Together, these create and maintain the additional social stigma of leprosy for women. Furthermore, the biological disadvantages that cause the negative evolution of the disease are made significantly worse by the added stigma created by gender and cultural bias against women (Figure 1). In this section, the general effects of gender and culture on leprosy for women will be discussed. However, in order to understand the social effect of leprosy for women, clear knowledge of their culture must be sought. An attempt to address the

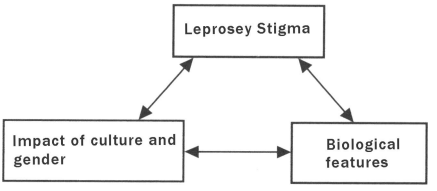

Figure 1. Components of the double jeopardy.

problem in such ways will minimize the tendency towards a eurocentric bias in ideologies, and preventative and remedial health programmes. Here, the emergence of gender bias within Indian and African cultures will be discussed to provide a backdrop for understanding the specific problems faced by female leprosy patients in these two geographical areas.

Women in India

In pre-colonial India, each religious community governed itself according to a body of local customs. The brahmins, India's highest caste, exercised the most control over women. Women were kept secluded and viewed as subordinate. Unable to marry out of caste, women served to maintain property within the caste and secure male positions in the social hierarchy. Primarily sexual control and the sexual purity of women governed the social respectability of men. The result, therefore, was a system whereby men, their family, and caste, gained social honour from women, thus reinforcing the need for women to be secluded and protected.

Indian family life today is as much governed by caste, class and gender as in the pre-colonial days. The political changes affecting Indian women have undoubtedly led to the formation of a modified family structure and support networks for women of higher caste and class. For those living in poverty and deprivation, namely lower castes and classes, fewer changes are to be found. Two types of family structure predominate, the nuclear family and the joint family. In the traditional joint family the new wife's primary relationship is with her mother-in-law. As a wife, a woman has obligations to her husband, her children and her mother-in-law. She is responsible, under the supervision of her mother-in-law, for domestic duties, caring for children and elderly family members, organizing rituals and festivals, and fulfilling social obligations towards friends and relatives. It is these duties that maintain the seclusion of women. From childhood, women have a socio-psychological disposition to believe that their role is within the home. In the lower social classes this structure remains. In the higher classes, where women may choose to, or be obliged to work, all these duties remain. In some families, structures may have been adapted to help the working wife and mother. Nuclear families became more common as young people moved to work in cities. Here, women have more power, but their duties remain the same, and they do not have the extended family to help them.

In brief, the preservation of male dominance in India has allowed only the minority of high social class women to strive for success. For the remainder, namely women of low caste and class, the male dominated world has been a constant for many hundreds of years. It is these women, who are uneducated, isolated, and living in poor conditions that are at higher risk of leprosy and its surrounding stigmata.

Women in Africa

For centuries, African society has centred on consanguineal families. Here, the notion of family is based on the enduring, separate kinship ties of men and women. Loyalty to kin outweighs the bond of marriage. Consanguinity was in the form of either matrilineal or patrilineal descent, where children of the marital union belonged to the female or male line, respectively. In matrilineal descent, for example the Swahili of Tanzania, male partners would live with females' families and in patrilineal descent, for example, the Tombo village people of Sierra Leone, females would move to the family compounds of the males. In addition to consanguinity, polygamy was also part of the culture. In many areas, men could take more than one wife and often lived in their own residence separate from their wives. They took no economic responsibility for supporting their wives. This led women to subsistence farming to support themselves and their children. Perhaps this has led to the western image of black African women as strong and hardworking and provides typical images of African women working the land with babies tied to their backs. Husbands, therefore, did not guarantee security as in the Indian culture. Instead, in African society, kin could always be called upon for economic support and, in addition, it was kin who inherited land not spouses.

In the above example, women lived side-by-side as co-wives. Often the first wife was the dominant female, who looked upon new wives favourably because they added to the workforce. However, women were not always given their hierarchical level automatically, and they had the added pressure of competition over attractiveness, domestic and economic activities, as well as the need to please their mother-in-law. Together, husbands and mother-in-laws exerted control over women who had to gain permission for everyday activities. Unfair treatment of women was combated by women's kin groups who had the power to pressurize men to modify their behaviours.

Women's relative power and independence in Africa began to slip away with the monetarization of the economy, urbanization, and colonial and post independence development policies.[8] All led to the involvement of men in a cash economy. Women and children had less cash earning potential due to their continued subsistence needs. Women's work lost prestige and became devalued, leaving them vulnerable. In the cash earning economy rural women could no longer barter for goods, and their workload increased to earn money. Husbands continued to expect women to look after their own needs in the same way as in the pre-cash economy. Gender inequality grew as men continued to earn cash, and being unable to support themselves, women became increasingly more dependent on men. Women no longer had their own rights within marriage because they and their kin were dependent on the same men for money.

The effect of urbanization was also to fragment descent groups and the kinship ties of older neighbourhoods. Kin groups could no longer function on a daily basis. Women began to find friendships and support out of their kin groups and sometimes across ethnic divides. In many ways, women could adapt to these changes, but there were new boundaries that took away much of their independence within the urban setting. They had no right to housing, and were therefore forced to live with their husbands. This removed privacy and created new strains on the marriage. Many women insisted on civil marriage ceremonies to prevent polygamy and shared income, but men continued to take unofficial wives. In East Africa, many men feared female independence and to a large extent controlled female income. The cash earning potential of girls and women in the urban economy was, therefore, still limited.

Female poverty, both rural and urban, created by monetarization, has left much of the female population of Africa in fear of destitution. This has led to high fertility levels to produce offspring that will provide social security by contributing to labour intensive activities. This has resulted in low levels of education, few skills, and low income, which in turn maintain high fertility rates. This vicious circle traps women in poverty and a life of male dominance.

To summarize, African and Indian women have both been moulded by their traditional nurturing roles, by colonial rule, and by western influences on their respective economies. Both groups of women are largely dependent on men and persistently bound to domestic activities and child rearing. In both continents, it is the women of the lowest social classes who have experienced the most restrictions on mobility, education, and personal finances. A critical outcome has been to engulf their lives in forms of poverty, which place them at particular risk from chronic diseases, like leprosy. Leprosy and its attendant risks, therefore, can only be studied and countered by assessing the problems and needs of these women within their own cultural backgrounds. The next section aims to address the culture and gender induced problems for women with leprosy in African and Indian society.

Social and cultural dimensions of leprosy for women

Global registered prevalence of leprosy in 1996 was 0.17 per 1000 population.[9] This figure was probably an underestimate because of wide differences between registered cases and actual numbers. World wide, the number of registered patients has reduced over the last 10 years,[10] but in India and Africa leprosy remained endemic. Prevalence rates in India and Africa were significantly higher than world-wide rates, at 5.9 per 10,000 population in India and from 7.79 (Central African Republic) to 0.09 (South Africa) per 10,000 in Africa.[11] Case detection rates vary from country to country, but in India and most of the rest of the world, rates were higher in males compared to females, producing a ratio of 2:1. In Africa the gender ratios reflected higher base detection rates for women than men. In Kenya, the gender ratio was 1:1,[10] with even higher rates for females in Uganda[12] and Malawi.[13] Why is there a difference in gender ratios between India and Africa? Is it that women in India are less exposed to leprosy in comparison to men than women in Africa? Do African women have less fear of stigmatization compared to women in India, leading them to seek medical care more frequently? Are medical services in Africa more accessible to women compared to India? These questions are addressed below.

Exposure to leprosy

Cultural diversity has resulted in different levels of female exposure to leprosy. In Africa, women's roles take them away from their family home. They often have sole responsibility for themselves and their children, which has led them towards subsistence farming and cash earning work in the community. In addition, African women are in contact with relatives outside their immediate family due to kinship ties. This takes them beyond their own communities to different settlements. It is this community contact that may result in more frequent exposure to leprosy.

In contrast, the role of Indian women has been within the domestic environment for many

hundreds of years. This seclusion limits their community contacts with leprosy. However, seclusion brings its own problems in leaving leprosy cases undetected for longer.[10] In countries like India, Ulrich *et al.*[14] have attributed the decreasing incidence of leprosy and the lower case detection rates amongst women not only to seclusion alone, but also to the decreased marriage opportunities for women with leprosy This limits reproductive activity, and consequently fewer children are born into high-risk leprous environments. Where women do marry, numbers of pregnancies tend to be limited to prevent the subsequent deterioration to women's health.

Across both continents there are common exposure problems for all women in the lower socio-economic groups. Specifically, lower socio-economic groups tend to have poor housing, inadequate ventilation, low nutritional status, and higher risk of leprosy contacts. Poor nutrition, in particular, can compromise immunological status.[14] Religious and culturally determined food habits can lead to specific deficiencies. In general, females have a high risk of iron deficiency anaemia, which causes increased susceptibility to disease. Intercurrent infection, more common in deprived groups, also leads to lowered immunity and a more serious risk of contracting leprosy. Female exposure to leprosy cannot, by itself, offer a full explanation of the incidence and prevalence of leprosy among women. For a fuller explanation, we need next to explore women's use of health services.

Utilization of health services

Access to and use of health services by women can be influenced in a number of ways: the availability of health care; literacy levels; awareness of the disease, and of available health care; family position and decision-making power; geographical and family mobility issues; the quality of health care provided; and the stigma associated with the disease.

The availability of health care is a critical aspect of early detection and treatment of leprosy. In 1988, the World Health Organisation Expert Committee on Leprosy recommended that leprosy control should be integrated into primary health care services. In making this recommendation, it was considered that health services would reach a greater proportion of the population. However, research from India suggests that detection rates in rural areas are much lower for women than men. In urban areas, detection rates are not significantly different between the sexes. These differences are related to lower health care coverage in rural areas.[15]

In combination, literacy and awareness levels have a key impact upon the utilization of health services. Specifically, if women have a poor understanding of causation, symptoms and available health care, then services, however efficient, will not reach the target population. In India, leprosy was traditionally thought to result from the 'wrath of god'.[16] This resulted in women delaying treatment until measures such as fasting and offerings had been made. This misconception has become less frequent, but new levels of awareness have not prevented delays in women seeking treatment.[17] In general, women in India have poor knowledge of the presenting symptoms of leprosy, and are less aware of the health services available to them than men.[18] It is likely that Indian women's poor knowledge of leprosy stems from a lack of education and the seclusion that is typical of Indian culture.

Similarly, African women often have a very traditional understanding of the underlying cause of leprosy. For example, it was thought that when people died, they became spirits. The spirits or 'muzimu' had to be appeased and made comfortable continuously because they became easily upset. If ignored or neglected, they could inflict leprosy on anyone, not necessarily the neglector. This belief led many African people to wear charms to ward off

the spirits.[19] 'Bad blood' reflects a modern understanding of leprosy, but is also felt to be the causative factor in sexually transmitted diseases and psychiatric illnesses.[19] However, specific knowledge of causation appears to be lacking in much of Africa, including north-western Botswana,[20] Ethiopia,[21] Congo and Tanzania.[22]

In Botswana, the clinical signs of leprosy were linked appropriately to skin lesions,[20] a contributory factor to early detection and health seeking behaviour. In contrast, awareness of symptoms and availability of services is poor among Nigerian females. This has been attributed to Nigerian culture, where spouses are the most important sources of information for women about leprosy.[23] However, it appears that among many African women, there is knowledge about modern healthcare availability, and there is a more universal belief that leprosy is curable. Moreover, traditional lifestyle and beliefs in African medicine have meant that modern healthcare ideas have been integrated into pre-existing health beliefs. This is particularly so for women, who are not educated to understand leprosy in a more modern way. African women are more likely to try over-the-counter remedies first, followed by traditional healers, and then health clinics, leading to delays in treatment. In brief, evidence suggests that both Indian and African women are less aware of causation, symptoms, and the availability of health care than men in each respective geographical area. This can be attributed to illiteracy and to socio-economic deprivation in both countries, and the continued seclusion of women in India.

The decision-making powers of women are determined by their status in the family structure. Indian women, particularly of lower caste and class, tend to have few decision-making powers in the home, and experience low social status in the family. They are controlled by their spouses in both joint and nuclear families, and frequently in the joint family structure by their mother-in-laws. Thus, health care decisions for women are often made by husbands or mother-in-laws. Research suggests that Indian women exhibiting early signs of leprosy often delay seeking medical attention because of their partners' apathy or their mother-in-laws' jealousy.[15] Delayed medical treatment can result in deterioration of the disease and a higher risk of deformity. In addition, while the disease remains active, other members of the family are at greater risk of infection.

In rural Africa, where women often have responsibility for the home, work and the upbringing of children, decision-making powers still appear to remain with men. Senior males make the majority of key decisions, including those about female healthcare.[20] In contrast to the male apathy of India, beliefs that leprosy is curable have resulted in community attitudes in Africa. Such attitudes encourage women to seek early treatment.[20] In brief, in much of India and Africa, the authority to make decisions regarding health care lies with men. In India, this culturally determined social framework has often hindered female leprosy patients. In contrast, evidence suggests that the attitudes of African men allow women to seek medical care more promptly.

The *geographical mobility* of women is limited by lack of decision-making power, time, money, an unwillingness to disrupt household duties, and the inability to find other caretakers for dependent elderly relatives and children.[10] Indian women in joint families have a potential advantage here, in that they may have relatives available to care for children and other dependants. However, this advantage is undermined by their lack of decision-making power, a lack of money, and an unwillingness to disrupt household duties. Traditionally Indian women have been moulded to believe that their role is within the family home caring for others. To spend time and money seeking personal health care may involve confrontations with husbands or mother-in-laws, and guilt from leaving family uncared for. The nuclear family structure may provide less flexibility for women because they do not have additional carers in the home. In

the higher social classes, however, women from nuclear families are more empowered, have more money available to them, and have servants to share household duties.

In Africa, the mobility of women is still restricted, but due to the cultural differences between India and Africa, the nature of the restrictions is different. African women have limited decision making powers, as outlined above. The positive attitude of their community towards seeking medical care and the practice of making alternative carers available, linked to other wives or kinship ties, offsets this. However, in terms of time and money, women have little of either. This is reinforced by their involvement in subsistence farming rather than the cash earning employment activities of men. It appears that the mobility of African and Indian women is limited, but that the limits are not the same for each group. This reflects their roles in two very different cultures.

The *quality of health services* available can provide major barriers for leprosy patients seeking health care. A problematic issue for females in general is the fear and embarrassment of having to see a male doctor. In western society women can choose to see female doctors if they wish, but in developing countries this service is not always available. By not catering for both sexes, health care services reflect a poor understanding of the needs of female patients. In India and parts of Africa, this lack of gender awareness is particularly problematic. The reason for this is two-fold. Firstly, a high proportion of health clinics are male dominated and secondly, women of certain religions are forbidden to see male doctors. After puberty, Islamic women are not allowed to show their bodies to any other man apart from their husband. In India, this problem may be reflected in case detection rates of males and females aged 11–17 years, where the female detection rate is half that of males.[10]

The *stigma* associated with leprosy acts as a barrier to seeking medical care. Women's fears centre on damaging their marriage prospects, losing their husband, children and homes, and inflicting the stigma associated with the disease onto their children. For men, the disease does not lead to such severe consequences. In India, women hide their symptoms for longer than men do for fear of stigmatization.[17] The outcome of leprosy diagnosis and related stigma is discussed below.

To summarize, relative to men, women in India and Africa are disadvantaged in their utilization of health care services. The culturally determined roles of women lead to lower levels of awareness of the symptoms of leprosy and available medical facilities. This is further aggravated by their inferior decision making power, poor mobility and a greater fear of associated stigma. Furthermore, health care services appear to reflect this gender bias, both in availability and specific services for women. This gender discrimination in society and health care services is reflected in a survey by Rao *et al.*,[17] where 85% of female leprosy patients felt that gender bias was definitely responsible for the delay in the detection of their disease. Interestingly, 67% of men agreed with this opinion. Below, the gender inequality is discussed in relation to case detection methods.

Case detection

Case detection is the organized and systematic search for patients in the community. Its intensification can only be justified if there is adequate facilities for treating a larger group of patients.[24] Case finding methods are broadly split into two types: active and passive. Passive case finding includes voluntary reporting, and referral and notification. Voluntary reporting requires community awareness of the signs and symptoms of leprosy, and an efficient and

reliable diagnostic and treatment service. However, its efficiency as a case detection method is impaired by the intense social stigma related to leprosy. For women in particular, voluntary reporting is limited further by lack of awareness and poor mobility

Active case finding methods aim to screen populations to find unreported cases of disease. There are two major types: general surveys and contact surveys. General surveys are useful in areas of high endemnicity, but are both expensive and time consuming. They involve either systematic house-to-house enquiry, or the gathering of populations to central points in villages. The first method ensures all women are seen; the second is open to the risk of female non-attendance. Contact surveys involve the surveillance of all contacts of high risk leprosy patients. This method has been found to be successful in areas of low and moderate endemnicity, where there is greater clustering of leprosy.[25] However, it only identifies a small proportion of new cases arising specific area.

Case detection methods show gender insensitivity.[10] Rao *et al.*[26] report poor detection of female cases through passive methods, and more effective detection through active case finding. This would reflect the low level of leprosy awareness amongst women, lack of mobility, and fear of stigmatization. Active case finding cuts across gender bias, ensuring female detection. There are specific case finding problems in India among females aged 11–17 years where examination by male medical staff is problematic.

Contrary to the evidence of Rao *et al.*[26], recommendations of the WHO Expert Committee on Leprosy[25] favoured self-detection through health education. This runs counter to the above evidence, and fails to take account of gender sensitivity in case finding. In addition to detection and diagnosis, gender differences in treatment compliance, as discussed below, are important in terms of health education programmes.

Treatment and compliance

The treatment of leprosy involves administration of antibacterial drugs (rifampin, clofazimine and dapsone; MDT). The aim is to kill *M. leprae* in the shortest possible period and prevent emergence of resistant strains of *M. leprae*.[17] Additional management of eye, nerve, hand and foot lesions involves physiotherapy, occupational therapy, and the ability to recognize serious manifestations of the disease for referral.

Evidence indicates that women are more compliant with drug treatment than men.[26] In India, female compliance may be a result of women having been socialized to conform to prescribed behaviours. However, the benefit of female compliance is perhaps outweighed by delay in seeking medical care.[17] It is interesting that Indian women often rely on traditional and spiritual healing as well as drug therapy. This may be a result of the poor understanding of treatment by women compared to men.[27] African women also combine modern treatments with traditional medicine. This is satisfactory because most traditional healers do not believe that modern and traditional African medicine should be mutually exclusive.[21]

Although female compliance is better than male complianceto drug therapy, it is Important to note that females are not 100% compliant. Indeed. Vlassof (in Le Grand[10]) found that 1000 of female leprosy patients in a leprosy colony in India were non-compliant, despite awareness of the need for treatment. A well documented problem with female compliance in India is the similarity of monthly packets of dapsone pills to oral contraceptive pill packaging, leading to conflict with mothers-in-law who want their sons to have children. Furthermore, compliance is hindered by difficulty in attending treatment clinics due to limited time, money and transport.

Outcome of diagnosis

Diagnosis of leprosy undoubtedly results in shock for individuals and their families. Men diagnosed with leprosy in India suffer fewer negative reactions, such as shame, fear, or blame from spouses. Women suffer from more negative reactions. Positive reactions, for example, sympathy and support, are rare for both sexes, but particularly so for women.[10] The power and influence of men within the family structure enables them to maintain their position in the household more frequently than women.[10] Women report being pressurized to leave the family home, but certain factors influence them to remain: strong marriages; husbands that are supportive in finding early treatment; prompt detection of the disease; seeking early treatment; and motherhood, which elevates women's status within the family.[27] However, under present law, it is easy for spouses to insist on separation (Muslim Marriage Act, 1939; Special Marriage Act, 1954; and the Hindu Marriage Act, 1955).[28]

Where women remain with their families, they are often banned from sleeping in the same room as their spouse and family. There is a particularly high discriminatory attitude towards women in joint families. This results in a move from joint to nuclear families after detection. This is particularly common in South India.[29]

Family reaction to leprosy diagnosis is not as well documented in Africa. It appears that, in the early stages, individuals remain well integrated in their families.[20] Later, as deformities develop, sexual relations are prohibited and divorce is easily secured.[19] The literature does not specify any gender bias, but it is interesting to find that in a survey of a Zambian leprosy colony, more males than females reported that their spouses left them after diagnosis.[19] This may be a result of women being less economically reliant on men in rural society than, for example, in India.

Beyond the marriage bond, the effects of leprosy diagnosis on the domestic environment of women are far reaching. Women in India often become isolated from domestic duties, especially cooking and caring for children. This has a devastating effect, since it is these roles that have come to shape women's self-identity. The freedom to touch and be touched, which acts as reinforcement for female caring roles, is also limited. This is enforced by spouses, or by women who voluntarily withdraw for fear of contaminating the rest of their family.[27]

African women appear to continue day-to-day domestic and farming duties. However, when deformities appear, both roles become very difficult and families may suffer as a consequence. In Ethiopia, an unwillingness to employ or work alongside leprosy patients has been documented.[21]

In India, community reactions to leprosy appear to discriminate between men and women. More women than men have constraints on social activities, travelling, and attendance at religious festival celebrations.[17] However, this isolation is often reinforced by women who remain aloof within the community to prevent passing the disease on to others.[28] In Africa there is little evidence to suggest a gender difference in community reaction to leprosy. Moreover, patients appear to be well integrated and accepted within the social structure of the community.[20] In contrast, a study in Ethiopia revealed an unwillingness to provide homes for or shake hands with people with leprosy.[21] This may reflect cultural differences between African communities.

Visible deformity often leads to a much more severe level of isolation for leprosy patients. In Africa, this isolation cuts across marriage bonds and kinship ties, and women are commonly expected to dissociate themselves completely from family.[19] In India, the fear

of deformity often results in women leaving their homes and family voluntarily, because without the use of their hands to perform domestic duties, they feel they are useless and a burden. In India, deformity primarily effects the hands of women and the feet of men, reflecting their respective roles indoors and outdoors.[10] In Africa, it may be that both the hands and feet of women become deformed as a result of their multiple roles.

In brief, the lower social status of females in India is causing women greater suffering as a result of leprosy, in terms of marriage, family, culturally defined roles, and isolation. For African women, gender bias in the outcome of leprosy is less well documented, but the evidence presented in this essay suggests that it exists and has detrimental effects. Below, the devastating effects of leprosy on marriage prospects are discussed, followed by the potentiating effect on leprosy of the cultural demands to produce children.

Marriage and children

Women with leprosy are less likely than men to have marriage opportunities.[30] In India, women with leprosy have had to make more compromises than men when choosing marriage partners. Women often marry men who are at least as deformed as themselves; in contrast, men occasionally marry healthy females.[27]

The gender bias and stigma associated with leprosy goes further than affecting women themselves to involve their children. Commonly, daughters have difficulty finding marriage partners. Up to 85% of women studied[27] left home to prevent their daughters from facing this discrimination.

Pregnancy

In India, it is women's duty to provide children for their husbands. Failure to do so may result in confrontations with husbands and mothers-in-law, and in some cases, separation and divorce. In Africa, children provide social security for women and higher status than other childless wives in polygamous marriages. This cultural pressure to bear children leads to deterioration in disease status and consequently more isolation from family and community. Women are therefore caught in a vicious circle: they experience isolation if they *do* have children and isolation if they *do not*.

Summary

There are cultural differences between the status of women in India and Africa. These result in differential levels of exposure to leprosy, differences in understanding about causation, and a range of male attitudes towards female uptake of health care services. However, the low socioeconomic status and gender bias towards female leprosy patients also means that there are important similarities in both cultures. Specifically, women have a poorer understanding of disease causation, knowledge about symptoms, and information available on health care than men. They are reliant on men for permission to seek medical care, and have limited mobility. They suffer more discrimination from spouses, family, work and the community. In addition, women the added biological and cultural disadvantages placed on disease status by

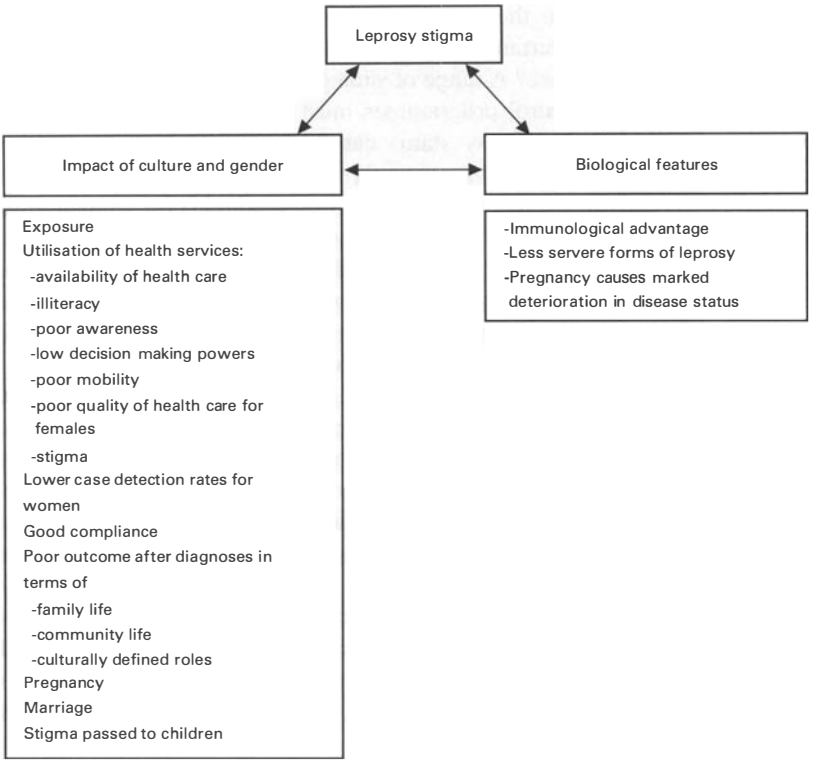

Figure 2. Components of the double jeopardy, expanded in light of discussion.

pregnancy. In brief, gender bias in India and Africa results in greater suffering for women with leprosy. This is reflected in the female under-utilization of health services, and the stigma and isolation specific to women that result from leprosy diagnosis. Furthermore, health services appear to reflect the gender bias in both the quality of services available and in case detection methods.

For Indian and African women with leprosy, the double jeopardy, therefore, is a combination of biological factors unique to women with a culturally defined gender bias, that results in more stigmatization and isolation for women (Figure 2). The culture and gender perspective therefore has very important implications for health prevention and promotion programmes.

Implications for health care

The evidence presented in this essay highlights the need to incorporate culture and gender perspectives into the health education and management programs for leprosy. Primarily, an approach based on cultural dynamics will promote better acceptance and an improved uptake of services. Moreover, a programme that incorporates gender specific issues for females will, theoretically, lead to improved detection rates and earlier treatment for women. This could be addressed at a number of levels: at the level of the *individual* – in terms of health beliefs; at the level of the *family* – linked to attitudes; and at the level of the *community* – in terms of local

beliefs. Improved strategies could then be targeted at health care availability; the gender insensitivity in health services; government policies; and health budget allocations. What would such a vision of health care look like? A range of strategies is needed to support such a vision.

First, the aims of leprosy control programmes must be defined before any recommendations about improving female leprosy status can be made. Leprosy prevention is the ultimate goal of control programmes, but is presently unobtainable due to the lack of effective immunization and continued world poverty. The next best method is for women to recognize their symptoms earlier, present at health clinics sooner, comply with treatment and prevent the emergence of disabilities. The evidence presented in this essay suggests that women are more disadvantaged than men in all these activities, except for compliance. Implicated in the culturally defined inferior status of women are higher rates of illiteracy, immobility, stigmatization, and a lack of gender sensitivity within health care.

Second, at the community level, the single most effective method of improving the rates of female leprosy detection and the accompanying prevention of associated social and physical disabilities is health education. Health education aims to promote a reasonable attitude towards leprosy that neither exaggerates nor minimizes the dangers of the disease.[24] It involves individuals, spouses, families, communities and health care professionals. Who provides health education? The answer is that all health care workers should be involved in health education, and themselves need to be given a wider understanding of leprosy and, in particular, the specific problems faced by female leprosy patients. Indeed, gender sensitivity in dealing with leprosy patients must be encouraged amongst health professionals at all levels. This includes physicians, social workers, paramedics, general medical doctors, community nurses, midwives and personnel dealing specifically with leprosy, for example, specialist doctors and leprosy nurses.

Third, health education should focus on educating women about leprosy in a culturally sensitive way, with specific objectives that will enable them to seek medical help, and reduce social stigmatization. Women need to be taught a number of fundamental facts about leprosy in order to undermine any preconceived ideas that could hamper its detection or women's attendance at health clinics. First and foremost, women must be able to recognize the presenting symptoms of leprosy, know that it can be cured with early treatment, and know where to go to get the treatment they require. Additionally, information about the causation of leprosy will provide a better understanding of the disease. After diagnosis, health education should centre on issues of compliance, deformity prevention and pregnancy. The biggest problem in educating women appears to be accessing them. Many methods have been suggested, for example community lectures by health workers, informative newspaper articles, talks on the radio, posters, pamphlets, booklets and film strips. All of these methods, however, require either literacy or mobility Other methods that may be more accessible to women include the formation of women's groups within villages with female teachers or female members of local government as educators.[17] It may also be possible to build upon female reliance on traditional medicine and religion by educating local healers and religious leaders to detect and refer leprosy cases: and to educate women about leprosy. The paramount issues, therefore, in health education for women are to make it accessible, understandable, and non-threatening. Once leprosy is diagnosed, health workers can continue to educate women about leprosy during their attendance at clinics for treatment, family visits and community talks.

Fourth, the health-education of women alone may not be enough to overcome the mobility problems or stigmatization specific to women. Specifically, lack of mobility and

poor decision-making powers can inhibit women from seeking care. Critically, it is not only women who require this type of education, but also their spouses and families. For example, if spouses have an understanding of the early symptoms of leprosy and the need for prompt treatment to promote cure, then they are more likely to allow women to seek health care. Family understanding could also help women to follow complicated drug regimens, and could encourage patients towards treatment compliance. Indeed, the real importance of family empathy may be in discouraging women from hiding their disease for fear of isolation and stigmatization.

Fifth, whole communities must be targeted with regard to health education if the stigmatization associated with female leprosy is to be reduced. It is the adverse reactions of communities to female leprosy patients that leads to the devalued status and social rejection of women. If local and national communities were to understand the cause, ease of treatment, and the consequences of a lack of community empathy, then perhaps women would feel less afraid of approaching leprosy health care services. It has been suggested[1] that the most effective method of reaching communities would be to educate all school age children. From this perspective, education is the key to developing societies which may, in the future, be less stigmatizing and more accepting. In addition to increasing community awareness of leprosy, opportunities to mobilize community resources and strengthen community co-operation are more likely to facilitate early recognition and to promote self-reporting by women. Where self reporting is ineffective, community willingness to carry out general or case contact surveys might be sought.

Health education is one of the ways of reducing gender bias associated with leprosy, and in turn, improving female detection rates. However, other strategies may need to be considered. Adapting existing health care services in order to achieve better levels of care for women with leprosy may also be important. Specifically, the education, clinical training, and employment of more female health care professionals would dilute the gender insensitivity of health care services. Women would feel more able to consult with, and be examined by other women. Indeed, the provision of female doctors may improve the poor detection rates of pubertal girls in India and parts of Africa. Once diagnosed, patients need to continue attending clinics for treatment. This causes particular problems for women due to poor mobility and little money. To respond, clinics must become more flexible to female needs, and provide treatment in places and at times convenient to women. If they fail to do so, compliance will not be maintained.

The stigmatization inherent in seeing doctors who care for leprosy patients can be dealt with at the community level with health education, but a shorter term and more immediate solution to this problem has been suggested.[27] It is proposed that doctors within primary health care systems should inquire about the condition of women's skin when trying to detect leprosy. It is suggested that this approach would be more acceptable to women, the hope being that the diagnosis and treatment of' skin disease would incur less rejection and isolation. This method may help women avoid the stigma associated with leprosy, but due care would need to be taken to continue to reduce leprosy discrimination within the community through the health education strategies discussed previously.

Finally, attention needs to be given to health education and management of female leprosy patients, specifically with regards to pregnancy. As discussed earlier, pregnancy is a very vulnerable time for women with leprosy, and there are risks of permanent nerve damage. Women need to be encouraged in control of their leprosy with MDT before considering having children. This may require the adoption of locally acceptable forms of contraception.

MDT should be continued throughout pregnancy, and women observed during pregnancy and lactation. In addition, health education is required to inform women of the signs and symptoms related to the reactions that can occur during these times. Help could also be provided to improve the survival chances of babies, thus enabling women to achieve their desired family size with fewer pregnancies.[5] In brief, women with leprosy require special attention before, during, and after pregnancy to prevent the lowering of disease status. Duncan[4] concludes that physicians dealing with such women should become more leprocentric, and less obstetrically minded.

Despite the limitations to change that are perpetuated by the existing economies of the developing countries where leprosy is endemic, employing health education and improved management plans can help to reduce the culturally defined, gender-specific disadvantages for female leprosy patients.

Conclusion

The culturally defined lower status of women in India and Africa has led to lower general awareness of the disease amongst women, poor utilization of health services, gender insensitivity in health care provision, and greater suffering for women with leprosy as a result of social stigmatization. The double jeopardy, therefore, has its roots in the culturally defined status and biological roles of women. In view of this, national leprosy control programs must continue to be very sensitive to the cultural backdrop of women, whilst at the same time encouraging women to attend health clinics by promoting health education and gender sensitivity with in health care. Indeed, one of the limitations of writing an essay that compares two continents is that it is very easy to generalize about culture across large geographical areas. It is important to note that there are marked intra-continental, as well as inter-continental differences between the experiences of women in India and Africa. This essay cannot hope to be precise enough to incorporate these differences, but aims to emphasize the general importance of the culture-gender perspective within leprosy research and control programmes.

Future research must look very specifically at the leprosy status of women with regard to individual cultures. It would also be interesting to investigate whether there is a gender bias associated with attitudes of the general public towards leprosy. Research that suggests that there is a greater female empathy and understanding towards leprosy would provide further evidence towards the need for female involvement in health care provision for leprosy, thus enhancing the female contribution to the expanding and developing societies that constitute India and Africa.

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Relapses in multibacillary leprosy patients: effect of length of therapy

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Summary Two groups of MB leprosy patients, one treated to the point of smear negativity (TSN) and the other given therapy for fixed duration (24 doses of WHO MB regimen) (FDT), were compared for relapse rates during treatment and in the post-treatment period. During the follow-up of 980·2 person years in 260 patients treated with FDT, 20 relapses (2·04/100 patient years) were observed. In the other group of 301 patients, who received therapy till smear negativity, 12 relapses in 1085·46 person years (1·10/100 patient years) occurred. Comparison of survival rates (without relapse) has shown that although there is no difference up to 4 years, the risk of relapse was significantly higher on longer follow-up in the FDT group. In addition, when patients were compared on the basis of initial bacterial load, it was found that the relapse rates in patients with BI ≥ 4 was significantly higher ($P < 0{\cdot}01$) in the FDT group as compared to those receiving treatment till the point of smear negativity (4·29 versus 1·27/100 patient years). All the relapsed patients responded to retreatment with the same drug combination, indicating that the exacerbation in their condition was because of insufficient treatment. It is suggested that to prevent or reduce relapses, treatment where feasible would be continued till smear negativity, at least in patients with high BI.

Introduction

Multi-drug therapy (MDT) was introduced in the treatment of leprosy in the 1980s and since then there has been a significant change in leprosy scenario both at the global and the national level. More than 8·4 million patients had been cured by MDT up to the beginning of 1997.[1] In India, the caseload of active patients has come down to less than 0·6 million from an earlier estimate of about 5 million, with many leprosy related parameters also having shown a downward trend.[2] This has been attributed to the high efficacy of MDT, in addition to increased political commitment and better supervision in the field. The early results with the use of drug combinations have been generally good, with very few practical problems.[3]

The success with MDT administered to the point of negativity in MB patients has encouraged workers to test shorter regimens of 2 years and even 12 months. The observation of continued clinical improvement and fall in BI, even after stoppage of treatment at the end

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of 2 years, and no relapses in the follow-up period,[4,5] resulted in 2 years fixed duration treatment (FDT) being recommended for field therapy of leprosy patients throughout the world.[6] Thus, FDT has been the mainstay of treatment of MB patients for the last 4–5 years and has been applied to all MB patients, irrespective of bacterial load and classification.

As in tuberculosis chemotherapy, in leprosy too, it is considered that the magnitude of relapses in the post-treatment follow-up period is an important parameter of efficacy and robustness of the regimen. Very low relapse rates in MB patients have been reported in several field studies carried out in different parts of the world.[1,3] However, of late, patients with relapses have been seen in many centres.[7–9]

MDT has been practised in the Central Jalma Institute for Leprosy, Agra. A large caseload of MB patients has provided an opportunity to study their response to MDT. In a prospective study, long-term follow-up after MDT has been made with the aim of detailing the course and progress of patients, and studying relapses, if any. An attempt has been made to delineate factors associated with occurrence or non-occurrence of relapses in the two groups of MB patients, one given FDT (for 2 years) and the other treated with the same regimen but up to the point of smear negativity (TSN).

Materials and methods

The study was conducted in two parts in a sequential manner. In one, the FDT group, 370 previously untreated MB patients who received 24 monthly doses of MB treatment, as recommended by WHO,[6] were included. The group included active IL, BL, BB and BT patients. Only those BT patients who were smear positive were included in the study group. A total of 287 patients took regular treatment and completed 24 doses within the stipulated 36 months. Of these, 260 were available to follow-up. Twenty-seven were lost to follow-up for reasons such as other illnesses (e.g. tuberculosis), migration or death due to other causes. The age of patients varied from 14 to 62 years (mean 39·1 ± 13·2); there were 242 males and 18 females. Patients had had their disease from 9 months to 7 years (mean 2·7 ± 1·4 years). Their disease classification and smear positivity, i.e. initial BI, is shown in Table 1. The smears were taken from four sites initially, during treatment and follow-up. Smears were repeated from the same four sites every 6 months during treatment and follow-up. However, when fresh lesions were suspected, these sites were included for smears. The mean of the four sites was taken as BI. All patients, while on treatment and after completion of FDT, were reviewed at least twice a year for clinical activity and bacteriological status.

The second part of the work comprised follow-up of 380 untreated lepromatous (BL/LL) patients in whom MDT had been given till smear negativity. A total of 301 patients were available for follow-up. The remaining 79 could not be followed up because of reasons such as migration or death. Their ages ranged from 13 to 59 years (34·5 ± 15·7). There were 30 females and the rest were males. The mean duration of illness in these patients was 3·82 ± 2·79 years. Mean BI, as detailed above, of more than 4 was observed in 210 patients, while 48 smears had a BI of 3·01–4·0 and the remaining 43 had a relatively low bacterial load with BI < 3. As stated, these patients had also been regularly monitored both during treatment, which was continued till smear negativity and in the post-treatment period. All patients of both groups, except one, had been clinically reviewed at least twice a year and smears repeated at least once a year during the follow-up period. For those patients who relapsed, the length of follow-up was taken up to the day of diagnosis of relapse.

In the present study, relapse was defined as increase of at least 2 log units BI at any site with or without the appearance of fresh lesions. Apart from the four sites as above, suspicious fresh lesions or suspicious erythema/infiltration was preferred for smears. Care was taken to differentiate relapse from reaction. Apart from insidious onset, asymptomatic nature, absence of systemic signs, increase in BI and lack of response to steroids were taken as criteria of relapse. If the lesions appeared suddenly, were associated with systemic symptoms or peripheral oedema and showed response to steroids, it was considered to be reaction and not relapse.

Statistical analysis was done using SPSS software and the K-M method of survival analysis was used for the two groups. Comparison of survival (without relapse) rates at different periods of observation (duration of treatment and follow-up) was done[10] to assess statistical significance.

Results

FIXED DURATION THERAPY (FDT) GROUP

As shown in Table 1, 162 (62·3%) patients in the group were of BL/LL type and 107 (41·2%) had a bacterial load of 4 or more. On completion of 2 years therapy, 120 of the 260 (46·2%) patients had become smear negative (Table 2). A larger proportion, 71·2% (109 of 153), of patients with BI of 3 or less had become negative in contrast to only 10·3% (11 of 107) of

Table 1. Bacterial load and classification of patients given FDT

	BI	BULL	BB	BT
≥4	58	0	0	58
3·01–4	47	2	0	4
2·01–3	32	2	8	42
1·01–2	25	5	27	57
>0-1	0	2	52	54
Total	162	11	87	260

Table 2. Progress of patients: time to reach smear negativity in FDT group

BI	No. of patients	Patients who became smear negative at 2 years		Time to become smear negative (months) [mean ± SD (range)]
		No.	%	
≥4	58	4	6·9	50·1 ± 11·4 (42–76)*
3·01–4	49	7	14·3	44·3 ± 8·2 (33–75)
2·01–3	42	16	38·1	38·2 ± 5·3 (31–47)
1·01–2	57	39	68·4	17·0 ± 2·2 (13–25)
>0–1	54	54	100	8·0 ± 1·2 (6–15)
Total	260	120	46·2	

*Three continued to be positive even at the end of 8th year.

Table 3. Details of relapses in patients given FDT

BI	No. of patients	Person-years follow-up	Relapses		Relapsed patients	
			No.	Rate/100 PY	Classification	Presentation
≥4	107	419·2	18	4·29	LL-13 BL-4 BB-1	Fresh lesions 4 Fresh infiltration 7 ENL 1 Smear +ve 6
<4	153	561	2	0·36	BB-1 BT-1	 Reversal reaction 2
Total	260	980·2	20	2·04	LL-13 BL-4 BB-2 BT-1	

highly bacillated patients (BI >4), showing complete clearance of bacilli. Follow-up after treatment stoppage revealed that even 6 years later, eight patients (all BL/LL with BI >4) were still positive and three of them continued to be positive even after 8 years of therapy. All other high BI patients showed a gradual decline in skin smear positivity, the BI coming down by 0·5–0·9 log units per year. Of the BT and BB patients, nine patients (all with initial BI of <2) continued to have active lesions for 1–3 years after completion of treatment, even though they had become smear negative in 12–18 months.

A total of 46 patients in this group developed reactions. Of the 19 BL/LL patients who had reactions, 12 had ENL and seven reversal reaction Two of the 19 had motor deficit. The remaining 27 with reaction were borderline leprosy (BB/BT) patients Six had more than one episode of reversal reaction. In 14 patients both skin and nerves were affected in reaction. Eight of the borderline patients had motor deficit. The patients were managed with thalidomide and those with reversal reactions given steroids, respectively, and all but five responded well. Of the five problem patients, three had recurrent ENL while in two, motor recovery was not complete.

Periodic examination over the next 2–8 years was done and each patient, except one, was seen at least twice a year. Follow-up of 980·2 patient years (3·77 ± 0·82) revealed that 20 had worsened bacteriologically, as evidenced by an increase in BI of more than 2 log units (2+) over the last reading, with or without clinical deterioration. This was taken as indicating relapse, giving an overall relapse rate of 2·04/100 patient years (or 7·7% during 3·7 years mean follow-up). Details of these are given in Table 3. Among the patients with BI ≥4, 18 relapses (4·29/100 patient years) were observed. Two relapses (0·36/100 patient years) were found in patients with BI <4, one each in patients with BB and BT leprosy. The relapse rate was thus significantly higher in patients with BI ≥4 ($P = 0·0002$). Of the total relapses, 17 occurred within the first 3 years of follow-up and the remaining three more than 5 years after stopping treatment.

In 11 of the relapsed patients, there was clinical evidence in form of fresh lesions (papules, plaques or infiltration), while in three, reaction (reversal reaction in two and ENL in one) was the first manifestation. Six patients were with relapse when smears showed a higher BI without any clinical signs. All the relapsed patients responded to reintroduction of the same MDT regimen (plus thalidomide or steroids in cases of reactions) and showed clinical regression and smear negativity within 2 years of restart of treatment.

Table 4. Length of treatment in BL/LL patients treated up to smear negativity

Treatment in years	Patients who became smear negative		
	No.	%	Cumulative %
<4	88	29·23	29·23
4–5	94	31·23	60·40
5–6	86	28·57	89·03
>6	33	10·96	100·00

Duration of treatment for smear negativity (mean) 4·9 ± 2·3 years.

TREATMENT TO POINT OF SMEAR NEGATIVITY (TSN)

As expected, in a majority of patients the treatment had to be continued for a long time. Details of length of treatment required to reach bacteriological negative state are shown in Table 4. The mean time taken to become smear negative was 4·9 ± 2·3 years. During treatment, reactions occurred in 116 patients (ENL in 105 and RR in 11, with two having both together).

A follow-up of 1085·46 years (mean 3·6 years) had been made in this group (Table 5). In the post-treatment period, though smear negative, nine patients suffered from ENL reactions. Eight had one episode of ENL, while the remaining patient had recurrent ENL. One patient had reversal reaction. During the follow-up, 12 relapses were seen. Thus, a relapse rate of 1·11/100 patient years (3·99% over 3·6 years mean follow-up) was observed. Ten relapses were diagnosed within 3 years of treatment stoppage. From Table 6, it is observed that 11 of the 12 relapses were in patients with initial large bacterial load (BI ≥ 4). Five of the 12 relapses were clinically silent and were detected on periodic smear examination, while four had fresh papules and in one, facial redness was the first sign. Two patients showed smear positivity when they came with ENL. All the relapsed patients were restarted on WHO MDT and 10 who continued treatment showed good response and became smear negative in 5–24 months, two having defaulted.

Table 5. Follow-up and relapses in patients treated till smear negativity

Follow-up (in months)	Patients	Person years follow-up	Relapse	
			No.	Rate/100 PY
<24	68	109·05	7	6·42
25–36	61	174·15	3	1·72
37–48	84	323·47	1	0·31
49–60	67	321·24	1	0·31
>60	21	157·56	0	0·31
Total	301	1085·46	12	1·11

Table 6. Details of relapses in patients treated up to smear negativity

BI	No. of patients	Person-years follow-up	Relapses		Classification	Presentation
			No.	Rate/100 PY		
≥4	258	866·45	11	1·27	LL-8 BL-3	Fresh papules 3 Facial redness 1 ENL 2 Smear +ve 5
<4	43	219·01	1	0·46	LL-1	Fresh papule 1
Total	301	1085·46	12	1·1	LL-9 BL-3	

Discussion

Field application of MDT in leprosy has been in progress for only 10–12 years and FDT for MB patients for even shorter duration of 4–5 years. Thus, follow-up of treated patients has not been long enough. Though early studies with short-term follow-up have shown good response, it is the long-term outcome of the treated patients that determines the ultimate utility of the therapeutic regimens. In leprosy, this has been possible in only a few centres.

Another aspect has been the continuously changing definition of MB patients. Initially only smear positive patients with BI >2 at any site belonging to BT and all active patients with BB, BL and LL classification were included in the MB group.[11] In view of the shortcomings in skin smear facilities at the field level, the definition was later modified to include all AFB positive patients of BT (irrespective of BI) in addition to others.[12] Subsequently, the MB group was enlarged to include all BT patients with more than five lesions as per WHO guidelines[1] and >10 lesions as suggested by NLEP, India.[13] Thus, in contrast to earlier studies on efficacy of MB treatment for multibacillary leprosy, the later ones include a substantial proportion of smear negative and/or low BI patients. Therefore, the outcome of recent studies is not comparable with initial trials in MB patients. In the present investigation, as was in practice at the time of start of work, only smear positive borderline (BT/BB) and lepromatous (BL/LL) patients have been taken.

The present study conducted with the aim of comparing the outcome of two regimens, differing in duration of treatment, primarily compares the number of relapses in two groups. For this, a uniform definition of relapse, as above, has been used. It is common observation that a significant proportion of MB patients, at the end of 2 years of FDT, are still smear positive and this is especially true for patients with BI on the higher side. Therefore, for diagnosis of relapse an increase in BI has been taken as the main criterion. For this, patients have been regularly followed up and examined at least twice a year and skin smears repeated. BI was compared with ears, earlier lesions or surrounding skin as the case may be. During follow-up, in patients who showed higher BI on one or more sites without any fresh or active lesion, repeat smears were done and assessed independently for confirmation. Because of certain problems, inoculation of mice could not be done for confirmation of viable organisms and drug susceptibility. However, response to repeat MDT, with same drug combination has been studied and taken as indirect evidence of both the viability and the susceptibility of *M. leprae* to drugs used as components of MDT.

The study has shown that in the group which was given FDT, there were 20 relapses in a follow-up period of 2–8 years (mean 3·77 ± 0·82), giving a relapse figure of 2·04/100 patient years (or 7·69% over a 3·75-year follow-up, approximately). The denominator here includes 87 BT and 11 borderline patients. Of these 98 patients, only three relapsed (relapse rate = 0·53/100 patient years), suggesting that therapy (2 years FDT) was adequate. Of the remaining 162 patients, all of whom belonged to the BL/LL group, 17 (10·5%) relapsed during the surveillance period, showing a significantly higher relapse rate as compared to BB/BT ($P < 0·02$). Of the total 20 relapses, 18 initially had a high BI of ≥ 4. In addition, all of them (18 patients) had a BI of > 3+ at the time of RFT, i.e. after 24 doses. Thus, in the group with high initial BI, a relapse rate of 4·20/100 patient years (overall 16·8%) was observed, which is significantly higher than in the group with BI < 4 ($P = 0·0002$). This indicates that within the MB group, patients differ in their response to treatment. While BT/BB patients and those with BI < 4 respond well, treatment seems to be inadequate for patients with a large bacterial load, mostly those with B/LLL disease.

A total of 46 patients developed reactions during the above follow up period; 34 had reversal reaction (seven BL/LL, 27 BT/BB) and the remaining had ENL. All belonged to the BL/LL group. The frequency is much higher than observed in field programmes. This is possibly on account of the larger proportion of patients continuing to be smear positive and may also be the result of clofazimine withdrawal on completion of FDT. There was no difference in the proportion of patients relapsing among patients with or without reactions in the post-treatment follow-up. Because of early diagnosis and management, very few patients, only two, had residual motor weakness. The observation of eight patients developing ENL in the post-treatment period highlights the fact that a significant proportion of patients with smear positivity, at the point of RFT, are likely to get reactions, and this therefore necessitates their regular follow-up at least to the point of their becoming smear negative. Further, detailed instructions to patients to visit the clinic early, if problems occur, can help in preventing deformities by early institution of anti-reaction treatment.

In the TSN group, of the 301 patients about 90% became negative in 6 years; the mean time for the smears to become negative was 4·9 ± 2·3 years (Table 4). Comparison of the decrease in BI in the two groups of the present study shows that the fall in the bacterial load appears similar, confirming that bacillary clearance is not affected by continued administration of the drugs (data not shown). Patients have been followed from 9 months to over 7 years after treatment stoppage. The occurrence of 12 relapses (Table 6) during the observation period gives a relapse rate of 1·10/100 patient years (or 3·99% over a mean follow-up period of 3·6 years). Here also, the majority of relapses were recorded within 3 years of treatment stoppage after smear negativity.

Periodic smear examination was found to be useful for detection of exacerbation, as this alone resulted in relapse diagnosis in five patients. One of the patients who attended the clinic after a default of 4 years, though clinically well, was found to be smear positive (3+) from the flank region, while smears from other sites were negative. Clinical signs of relapse were found in five and ENL as the first manifestation in two patients. Of the 12 relapses seen in the TSN group, 11 were among the patients with BI ≥ 4 (Table 6) and occurred during the follow-up period of 866·45 patient years, giving a relapse rate of 1·27/100 patient years. This indicates that among patients treated up to the point of negativity, the relapse rate as in EDT, was more in patients with BI ≥ 4 than those with smaller bacterial load, though the difference within the TSN group was not significant. When compared, with patients given FDT, the

Table 7. Comparison of survival (without relapse) rates, in the two treatment groups

Duration of treatment & follow-up	Fixed duration therapy (FDT) group		Up to smear negative group		
	Cumulative survival	SE	Cumulative survival	SE	*P*-value
36	0·9960	0·0040	0·9965	0·0035	0·94
48	0·9874	0·0072	0·9965	0·0035	0·267
60	0·9731	0·0108	0·9965	0·0035	0·047
84	0·8973	0·0250	0·9623	0·0071	0·0188
96	0·8500	0·3275	0·9536	0·0131	0·0055
120	0·8121	0·0409	0·9369	0·016	0·0067

relapse rate is lower among who had been treated till the smear negativity (2·04 versus 1·10/100 patient years). Survival analysis has been done to compare relapse rates in the two treatment groups (Table 7, Figure 1). Comparison of survival (without relapse) has been made up to 10 years, including the initial period of treatment (2 years in FDT and till smear negativity in the other group). There was no difference in the risk of relapse up to the fourth year; however, subsequently the hazard (relapse) risk was significantly higher in the EDT group, especially on longer follow-up. The difference is likewise larger when comparison is made of high BI patients in the two groups (4·29 in EDT versus 1·27/100 patient years in the

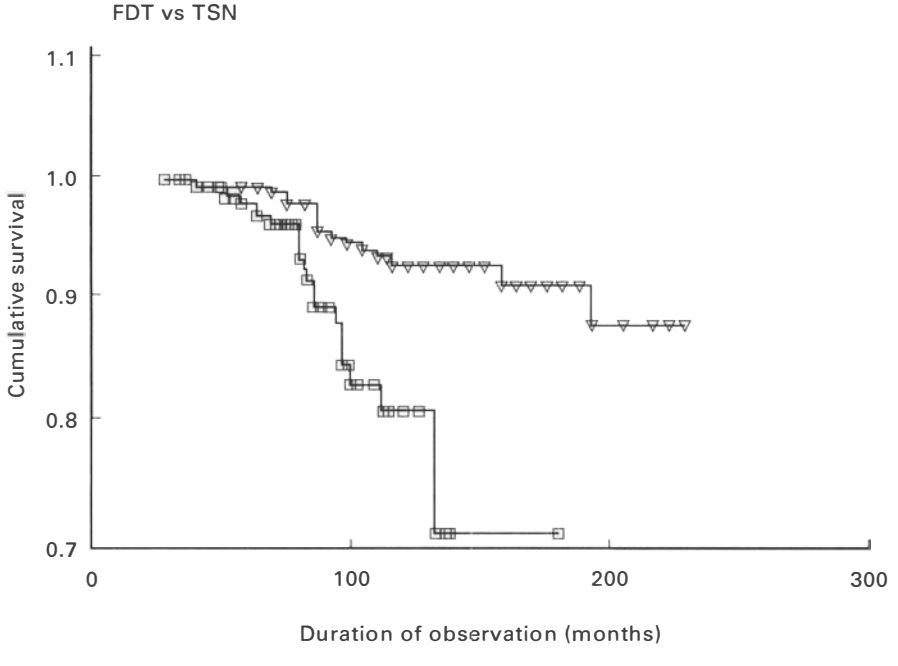

Figure 1. Comparison of survival (without relapse) rates in two treatment groups, FDT (□) and TSN (▽).

TSN group) and this difference was statistically significant ($P < 0{\cdot}01$). This indicates that relapses are fewer when longer treatment up to smear negativity is given and that the initial bacterial load, as well as BI, at the end of 2 years (figures not shown), is well correlated with relapses. This offers an explanation for the low relapse rates in many of the field studies, wherein the MB group of borderline patients who have been taken in on the basis of a larger number of lesions and/or are only marginally smear positive. Another explanation could be a better follow-up and periodic smears done in these trial groups as compared to the field studies, apart from the fact that the study was focused on the issue. Unlike, the report of Jamet *et al.*,[14] fewer relapses have been seen, even though there were larger numbers of patients with high BI in both the cohorts. This may be because of the relatively shorter follow-up in the present trial. Based on their experience[14] that number of relapses goes up steeply with increasing length of follow-up and projection of hazard risk, patient are being kept under surveillance.

From the satisfactory outcome of retreatment with same drugs, it can be concluded that the relapses were a result of persistence of drug-sensitive organisms which might have escaped the action of drugs, as has earlier been shown in both THELEP studies[15] and in our own work.[16] Higher relapse rate in the 2 year FDT group could therefore mean that not enough therapy had been given to kill all the organisms. This is in line with Pattyn's suggestion[17] that relapses in leprosy are biphasic, early relapses resulting from inadequate therapy while the late relapses may be the outcome of reactivation of persisters or reinfection. Indeed, our observations point to the relative earlier occurrence of relapses. It can be seen that in 15 of the 18 relapses in high BI (≥ 4) patients in the FDT group and in 10 of the 12 long-term treatment patients, relapses occurred within 4 years of stopping treatment, suggesting that therapy was not able to kill all the viable organisms.

The present study has shown that short course treatment (FDT), especially for high BI patients, is not adequate in reducing the relapses in the follow-up period, as earlier reported.[13] Since a majority of relapses were in patients with BI ≥ 4, it would be better to continue treatment for a longer period, at least in this group. Since the BI in almost all patients had come down to ≤ 2 by 4–5 years, in highly bacillated patients treatment should be continued for another 2 years, as has been proposed by Waters.[18] Thus, by the time they are released from treatment, the remaining number of bacteria will be small and the chances of any surviving *M. leprae* would be minimized. Since almost all high BI patients belonged to the BL/LL group, in places where smear facilities are not adequate, classification of patients could be taken as a guide. Thus fresh (untreated) patients with nodules, infiltration and/or numerous small symmetrically placed lesions and multiple symmetrically thickened nerves should receive longer treatment. In the field especially, where MDT activities have been going on for several years, the number of highly positive patients is not likely to be very large and therefore, a longer treatment for the few is feasible and should be considered. One may argue against this, as the relapses are due to drug (rifampicin, clofazimine and dapsone) sensitive organisms and could be retreated as and when they occur. However, when one considers the proportion in which relapses have been observed (Jamet *et al.*[15] and this study) and the impact of treatment failure on acceptance of therapy, a policy and recommendation for longer treatment appears justified for the group of patients with higher bacillary load (BI ≥ 4). Further, in view of frequent reactions, periodic follow-up until the patients become smear negative must be continued, as it would not only be beneficial in reducing deformities but also help in early diagnosis of relapses, if they occur.

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The treatment of acute nerve function impairment in leprosy: results from a prospective cohort study in Bangladesh

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Summary In this paper, the outcome of 132 patients having acute nerve function impairment (NFI) is reported at 4 and 12 months after the start of prednisolone treatment. In all, 68% of sensory nerves and 67% of motor nerves showed improvement at 12 months, with no statistical difference in responsiveness of various nerves to prednisolone. Duration and severity of impairment were not found significant predictors of treatment outcome. A core of 32% of impaired nerves did not respond to prednisolone, and 12% of impaired nerves had functional deterioration despite treatment. The mean eye-hand-foot (EHF) score improved from 2·02 to 1·33 in the treatment group (median score improved from 2 to 1). Approximately one-third of all patients requiring prednisolone treatment did not receive it, an important reason being that some patients developed new NFI against a background of chronic impairment, and were thus overlooked. The 'unjustly untreated' group of patients had a spontaneous sensory nerve function improvement rate of 62% and a motor nerve function improvement rate of 33% at 12 months from onset of NFI. The EHF score showed no statistically significant improvement.

Introduction

There is a wide literature reporting the response of nerve function impairment (NFI) and leprosy reactions to treatment with corticosteroids, and the topic has recently been reviewed.[1] In the past few years, there has been a shift towards the ambulatory treatment of reactions and nerve damage and a movement away from hospital based treatment,[2–6] and standardized or semi-standardized corticosteroid regimens have been used more widely.[2,5,6] In addition,

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there has been a movement both towards the recognition of NFI as a primary indication for treatment, and away from the clinically more obvious 'reactions'.[5–7] There is an increasing recognition that corticosteroids as a form of therapy have limitations, and that other treatment modalities should be explored.[1,8] However, despite this, corticosteroids remain the mainstay of treatment, and the most recent WHO Expert Committee on leprosy confirmed this by stating that '*most reactions and neuritis can be treated successfully under field conditions with a standard 12-week course of prednisolone*'.[9]

Despite the large amount of literature on the treatment of reactions, there are no controlled trials reported on the use of corticosteroids to treat leprosy reactions or NFI. Steroid treatment was introduced at a time when this type of study was unusual, and the drug's value was apparently so clear that it became unethical to consider carrying out such a trial. Most studies that have been carried out are retrospective in nature, and this is a weakness. Variations in the use of terminology also present a problem, making it difficult to compare studies. In addition, different measurement techniques have been used in the studies assessing nerve function, which introduces a further complication.

The Bangladesh Acute Nerve Damage Study (BANDS) is a prospective cohort study designed to investigate the epidemiology of nerve function impairment (NFI) in leprosy patients, its risk factors and response to treatment.[10] BANDS is based at a single centre in Bangladesh, the Danish Bangladesh Leprosy Mission (DBLM). This paper describes the response to treatment by corticosteroids of cohort patients who developed acute NFI.

The treatment of NFI and leprosy reactions at DBLM is largely field-based. This policy follows a successful pilot study carried out in 1994 in part of the DBLM project area to investigate the feasibility and effectiveness of such a system.[5]

The present study is prospective in nature and uses standard measures of nerve function that are common to all the studies being carried out in BANDS giving both continuity and consistency to the results.

Materials and methods

STUDY GROUP

The study group was the BANDS cohort. The 2664 patients, recruited over a 12-month period, comprised 1481 males (56%) and 1183 females (44%). Of these, 2220 (83%) of the patients were paucibacillary (PB), and 444 (17%) were multibacillary (MB).

Patients developing NFI either by registration time or during the first 12 months of follow-up were assessed initially in the field by trained leprosy control assistants, supervisors and physiotechnicians.[10] The patients were then either given treatment by staff in the field using corticosteroids in standard doses, or referred to hospital where necessary.

DEFINITIONS OF NFI

NFI was defined as follows:

Sensory NFI: reduction by ≥ 2 points in the sensory distribution of any one nerve, as tested by ballpoint pen. The following nerves were tested for sensory function: ulnar (five sites), median (seven sites), posterior tibial (11 sites). The positions of the test sites were shown in an earlier paper.[10]

Motor NFI: reduction by ≥2 in the MRC grade of the movement tested of any one nerve. Nerves tested for motor function were: facial, ulnar, median, radial, lateral popliteal.[10]

TREATMENT

The standard prednisolone regimen used in the field for the treatment of NFI amongst adults was as follows: 40 mg, 4 weeks; 30 mg, 2 weeks; 25 mg, 2 weeks; 20 mg,2 weeks; 15 mg, 2 weeks; 10 mg, 2 weeks; 5 mg, 2 weeks. The total length of treatment was 16 weeks. The dosages were reduced for patients with body weight <35 kg. Patients were referred to hospital if they had motor paralysis requiring intensive physiotherapy, or if they had concomitant complications or conditions such as neuropathic ulcers, anaemia, intercurrent infection or pregnancy. In addition, patients failing to respond to prednisolone were referred to hospital. In hospital, prednisolone was usually continued in the dosages mentioned above, but occasionally doses as high as 80 mg/day were used, treatment being titrated against response

Patients developing leprosy reactions in the absence of NFI were also treated with prednisolone, and sometimes other agents including aspirin and clofazimine were prescribed in accordance with the project treatment guidelines. However, only patients with NFI are considered in this study.

Patients were followed up in the field and in hospital, and their nerve function scores were recorded. From this, records at 4 and 12 months after starting prednisolone therapy were analysed, and the findings are reported in this paper.

OUTCOMES

Outcome was expressed in two broad ways. Firstly, the result of treatment of sensory and motor functions for individual nerves was given at 4 and 12 months, using the following definitions:

- *Full recovery*: restoration of sensory or motor score to normal.
- *Partial recovery*: improvement in sensory or motor score by ≥2 points, but less than full return to normal.
- *Same*: no change in sensory/motor score, or change by only 1 point.
- *Deterioration (worse)*: deterioration in sensory or motor score by ≥2 points.

Outcomes were expressed as simple proportions, using Epi Info software to determine the Fleiss quadratic 95% confidence intervals (CIs). In addition, a dichotomous definition of outcome was used: 'Improvement' included 'full' and 'partial' recovery of function, and 'Same or Worse' included 'same' and 'deterioration'.

Nerves were divided into two groups depending on whether the nerve was 'severely' affected or not. For motor function, MRC grades 0 or 1 (i.e. paralysis) were taken as severe, and grades 2 and 3 as mild. For sensory function, a reduction in 3+ points in the ulnar (maximum 5 points) or median (maximum 7 points) nerve distribution, or 5+ points in the posterior tibial (maximum 11 points) nerve distribution was taken as severe. Mild sensory loss was a 2-point reduction for the ulnar and median nerves, and a 2- to 4-point reduction for the posterior tibial nerve.

Patients were divided into two groups, 0–1 month duration of nerve damage and 2–6 months duration, based on a report that patients with <1 month duration of nerve damage recover better than those with longer duration of damage.[6]

Secondly, average EHF scores were calculated. The WHO disability grading system applies a score of 0, 1 or 2 to each limb and eye, and the overall disability grade is usually determined by the part of the body with most damage.[11] However, the individual body part scores could be added to give a sum 'EHF' score that expressed the level of impairment with more accuracy.[12–14] In this system, a score of 0 indicates no impairment, and the maximum score of 12 indicates visible deformity of both hands and feet combined with, for example, bilateral lagophthalmos and blindness. Mean EHF scores were calculated at registration, 4 and 12 months, and Student's *t*-test used to find the CIs for differences between means. In the calculation of the disability grade for eyes, the most recent WHO definition was used which assigns all lagophthalmos to grade 2.[9]

TREATED AND UNTREATED PATIENTS

In addition to the group of patients treated for NFI, another group was identified that according to the criteria should have received prednisolone treatment but for various reasons did not do so. The development of NFI in these 'unjustly untreated' patients has been analysed in a similar way to the treated group. The 'unjustly untreated' patients cannot be considered a true control group because of a lack of randomization. Nevertheless, because of the considerable importance of these patients, the outcomes of both groups are compared and discussed.

Results

OVERVIEW OF PATIENT GROUP

A total of 214 patients were identified who developed NFI within the first 12 months of follow-up. Of these, 90 had NFI present at registration, and 124 developed NFI requiring prednisolone treatment during the first year after registration. Thirty-seven patients out of 214 required hospital admission for treatment, the remainder being treated 'in the field'. At 4 months after the start of prednisolone treatment, 186 records were available for analysis, but by 12 months, follow-up records were complete for 201 (i.e. 15 patients did not attend clinic at 4 months, but did so by 12 months). Of the 13 patients lost to follow-up at 12 months (6% of the total), there were: 11 males and two females; eight MB and five PB; 13 adults; six received prednisolone and seven did not.

A group of patients was identified who should have received prednisolone for NFI but did not do so. In all, 132/201 (66%) patients received prednisolone, and 69/201 (34%) did not. Table 1 compares the two groups for sex, leprosy group, age, severity of NFI (see definition at foot of table) and duration of NFI (0–1 months and 2–6 months) with χ^2 and *P*-values given. For sex, leprosy group and age the treated and untreated groups do not differ materially, *P*-values being >0.3 for each χ^2 test. However, the groups differed significantly in the proportions of patients with short/long duration and mild/severe NFI, with a *P*-value of <0.05 for both variables in the χ^2 test. There is a significantly higher proportion of patients with short duration NFI and severe NFI in the *untreated* group.

OUTCOMES AT 4 AND 12 MONTHS

Table 2 shows outcomes at 4 and 12 months, respectively, for the eight nerve function modalities (facial motor, ulnar sensory and motor, median sensory and motor, radial motor,

Table 1. Comparison between treated and untreated patient groups

Category	Factor	Treated group	Untreated group	Total	χ^2	*P*-value
Sex	Male	95 (72)	47 (68)	142 (71)	0·32	0·57
	Female	37 (28)	22 (32)	59 (29)		
Leprosy group	MB	74 (56)	39 (56)	113 (56)	0·00	0·95
	PB	58 (44)	30 (44)	88 (44)		
Age group	Adult (15+)	124 (94)	67 (97)	191 (95)	0·96	0·33
	Child (<15)	8 (6)	2 (3)	10 (5)		
Duration of NFI	0–1 months	83 (63)	55 (80)	138 (69)	5·97	0·015
	2–6 months	49 (37)	14 (20)	63 (31)		
Severity of NFI*	Mild	47 (36)	14 (20)	61 (30)	5·03	0·025
	Severe	85 (64)	55 (80)	140 (70)		
Total	All	132 (66)	69 (34)	201		

* Severe NFI = presence of any of the following: MRC grades 0, 1 for any motor nerve tested; or 3+ sensory point reduction for ulnar/median nerve distribution; or 5+ sensory point reduction for posterior tibial nerve distribution.

Mild NFI = patient with no nerve having severe NFI as defined above.

Figures in brackets are percentages.

lateral popliteal motor and posterior tibial sensory) using the outcomes of full recovery, partial recovery, same and worse. 95% CIs have not been given for the outcome of the function of individual nerves, since the numbers are small and the resultant CIs have wide limits.

There was a higher proportion of nerves with *full* recovery amongst the treated group than the untreated group. At 12 months, 33% (23–44) of the treated motor nerves had recovered fully compared with 8% (2–24) of the untreated ones; 37% (30–45) of the treated sensory nerves had recovered fully compared with 17% (10–29) of the untreated ones. Proportions with full recovery amongst the individual nerve function modalities show higher levels of full recovery for the facial nerve (53% at 4 months, 58% at 12 months) and the median sensory modality (59% at 4 months and 62% at 12 months). However, numbers are small.

Amongst individual nerve modalities there was a fairly uniform level of improvement, but the facial nerve (82% at 12 months) and ulnar sensory modality (84% at 12 months) recovered slightly better than the other nerves, and the lateral popliteal responded least well (47% at 12 months).

Using the broader 'improvement' and 'same or worse' categories, amongst nerves with motor NFI, 74% (63–83) showed improvement at 4 months, sustained amongst 67% (56–77) at 12 months. This compares with 20% (8–39) improving without treatment at 4 months, rising to 33% (19–51) at 12 months. For sensory function, the overall proportion improving at 4 months was 73% (65–80), falling to 68% (60–75) at 12 months. Forty-five percent (33–58) of the untreated group showed sensory improvement at 4 months and 62% (50–73) at 12 months after being diagnosed with acute NFI.

A substantial proportion of patients did not benefit from prednisolone treatment. Overall, 32% (25–40) of nerves with sensory impairment and 38% (27–50) of nerves with motor impairment either had the same level of function at 12 months, or they had deteriorated. Thirteen percent (9–20) of nerves with sensory NFI and 12% (5–22) of motor function of nerves had actually deteriorated despite treatment.

Table 2. Outcome of treatment of NFI at 4 (A) and 12 (B) months shown by nerve

A

		Outcome at 4 months					Outcome at 4 months—proportions							
Nerve	Treatment status	Full recovery	Partial recovery	Same	Worse	Total	Full recovery	*95% CI*	Partial recovery	*95% CI*	Same	*95% CI*	Worse	*95% CI*
Facial (M)	Treated	10	6	2	1	19	0·53		0·32		0·11		0·05	
Ulnar (M)	Treated	7	19	9	2	37	0·19		0·51		0·24		0·05	
Median (M)	Treated	4	3	1	1	9	0·44		0·33		0·11		0·11	
Lateral popliteal (M)	Treated	3	8	5	0	16	0·19		0·50		0·31		0·00	
Radial (M)	Treated	0	1	0	0	1	0·00		1·00		0·00		0·00	
Ulnar (S)	Treated	12	12	5	1	30	0·40		0·40		0·17		0·03	
Median (S)	Treated	19	5	5	3	32	0·59		0·16		0·16		0·09	
Posterior tibial (S)	Treated	26	42	21	8	97	0·27		0·43		0·22		0·08	
All sensory nerves	Treated	57	59	31	12	159	0·36	*0·29–0·44*	0·37	*0·30–0·45*	0·19	*0·14–0·27*	0·08	*0·04–0·13*
	Untreated	5	23	27	7	62	0·08	*0·03–0·19*	0·37	*0·25–0·50*	0·44	*0·31–0·57*	0·11	*0·05–0·22*
All motor nerves	Treated	24	37	17	4	82	0·29	*0·20–0·41*	0·45	*0·34–0·56*	0·21	*0·13–0·31*	0·05	*0·02–0·13*
	Untreated	4	2	22	2	30	0·13	*0·04–0·32*	0·07	*0·02–0·31*	0·73	*0·54–0·87*	0·07	*0·04–0·32*

B

Nerve	Treatment status	Outcome at 12 months					Outcome at 12 months—proportions							
		Full recovery	Partial recovery	Same	Worse	Total	Full recovery	*95% CI*	Partial recovery	*95% CI*	Same	*95% CI*	Worse	*95% CI*
Facial (M)	Treated	11	5	1	2	19	0·58		0·26		0·05		0·11	
Ulnar (M)	Treated	8	17	8	4	37	0·22		0·46		0·22		0·11	
Median (M)	Treated	4	3	3	0	10	0·40		0·30		0·30		0·00	
Lateral popliteal (M)	Treated	4	4	6	3	17	0·19		0·25		0·38		0·19	
Radial (M)	Treated	1	0	0	0	1	1·00		0·00		0·00		0·00	
Ulnar (S)	Treated	14	10	5	2	31	0·45		0·32		0·16		0·06	
Median (S)	Treated	21	3	6	4	34	0·62		0·09		0·18		0·12	
Posterior tibial (S)	Treated	27	38	20	16	101	0·27		0·38		0·20		0·16	
All sensory nerves	Treated	62	51	31	22	166	0·37	*0·30–0·45*	0·31	*0·24–0·38*	0·19	*0·13–0·26*	0·13	*0·09–0·20*
	Untreated	12	31	18	8	69	0·17	*0·10–0·29*	0·45	*0·33–0·67*	0·26	*0·17–0·38*	0·12	*0·05–0·22*
All motor nerves	Treated	27	29	18	9	83	0·33	*0·23–0·44*	0·35	*0·25–0·46*	0·22	*0·14–0·32*	0·11	*0·05–0·20*
	Untreated	3	9	21	3	36	0·08	*0·02–0·24*	0·25	*0·13–0·43*	0·58	*0·41–0·74*	0·08	*0·02–0·24*

OUTCOMES FOR SEVERITY OF IMPAIRMENT

Table 3 shows outcomes of treatment for severity of symptoms. At 12 months, 48% (32–64) of mildly affected sensory nerves recovered fully compared with 34% (26–43) of severely affected sensory nerves; 41% (24–59) of mildly affected motor nerves recovered fully compared with 27% (16–42) of severely affected motor nerves. Overall, 44% (33–57) of mildly affected nerves recovered fully compared with 32% (25–40) of severely affected nerves. However, none of these differences is significant at the 5% level.

There was little difference between the overall outcomes, with 63% (46–77) of mildly affected sensory nerves showing improvement at 12 months, compared with 70% (61–78) amongst severely affected sensory nerves. Sixty-nine percent (50–83) of mildly impaired motor nerves showed improvement at 12 months compared with 67% (52–79) amongst severely affected motor nerves. Overall, 65% (53–76) of mildly affected nerves (sensory and motor) showed improvement at 12 months compared with 69% (61–76) of the more severely affected nerves, but this is not a statistically significant difference.

OUTCOMES FOR DIFFERENT DURATIONS OF SYMPTOMS

Table 4 shows outcomes for duration of symptoms. Once again, there is little difference in outcome between the two groups. A confusing picture is presented, with shorter-duration sensory impaired nerves apparently showing *less* full recovery than longer-duration impaired nerves at 12 months, i.e. 34% (24–46) versus 43% (32–55); but with motor nerves showing the reverse picture, i.e. 39% (25–55) of shorter-duration impaired nerves fully recovered versus 24% (12–42) of longer-duration impaired nerves.

The picture with regard to deterioration of function is also confusing, with 20% (13–30) of the shorter-duration sensory impaired nerves deteriorating in function, but with only 5% (2–13) of the longer-duration impaired nerves doing so; and with 11% (4–24) of the shorter-duration motor impaired nerves deteriorating in function, and 11% (4–26) of the longer duration motor impaired nerves.

EHF SCORES

The starting mean EHF score was higher for the untreated group ($2{\cdot}32 \pm 0{\cdot}22$) than the treated ($2{\cdot}02 \pm 0{\cdot}21$). There was a statistically significant improvement in mean EHF score for the treated group to $1{\cdot}19 \pm 0{\cdot}21$ by 4 months, rising slightly to $1{\cdot}33 \pm 0{\cdot}27$ by 12 months. There was a gradual, but statistically insignificant, reduction in mean EHF score for the untreated patients to $2{\cdot}18 \pm 0{\cdot}22$ by 4 months and $2{\cdot}13 \pm 0{\cdot}25$ by 12 months. The median EHF score was 2·00 for both the treated and untreated groups, remaining unchanged in the untreated group at 4 and 12 months, but improving to 1·00 in the treated group at both 4 and 12 months.

Discussion

OVERALL RECOVERY

The overall levels of recovery amongst the treated patients [overall improvement of 67% (56–77) amongst motor nerves and 68% (60–75) amongst sensory nerves at 12 months] are of a very similar order to those found in other studies. A previous study at DBLM found

Table 3. Outcome of treatment of NFI by severity of NFI symptoms at 4 (A) and 12 (B) months

A

NFI severity	Nerve modality	Outcome at 4 months					Outcome at 4 months							
		Full	Partial	Same	Worse	Total	Full	*95% CI*	Partial	*95% CI*	Same	*95% CI*	Worse	*95% CI*
Mild[a]	All sensory	19	10	6	4	39	0·49	*0·33–0·65*	0·26	*0·14–0·42*	0·15	*0·06–0·31*	0·10	*0·03–0·25*
	All motor	9	16	5	2	32	0·28	0·14–0·47	0·50	*0·32–0·68*	0·16	*0·06–0·34*	0·06	*0·01–0·22*
Severe[b]	All sensory	38	49	25	8	120	0·32	0·24–0·41	0·41	*0·32–0·50*	0·21	*0·14–0·29*	0·07	*0·03–0·13*
	All motor	15	21	12	2	50	0·30	0·18–0·45	0·42	*0·28–0·57*	0·24	*0·14–0·38*	0·04	*0·01–0·15*

B

NFI severity	Nerve modality	Outcome at 12 months					Outcome at 12 months							
		Full	Partial	Same	Worse	Total	Full	*95% CI*	Partial	*95% CI*	Same	*95% CI*	Worse	*95% CI*
Mild[a]	All sensory	19	6	6	9	40	0·48	*0·32–0·64*	0·15	*0·06–0·31*	0·15	*0·06–0·31*	0·23	*0·11–0·39*
	All motor	13	9	4	6	32	0·41	0·24–0·59	0·28	*0·14–0·47*	0·13	*0·04–0·30*	0·19	*0·08–0·37*
Severe[b]	All sensory	43	45	25	13	126	0·34	0·26–0·43	0·36	*0·28–0·45*	0·20	*0·13–0·28*	0·10	*0·06–0·17*
	All motor	14	20	14	3	51	0·27	0·16–0·42	0·39	*0·26–0·54*	0·27	*0·15–0·42*	0·06	*0·02–0·17*

[a] Mild NFI = patient with no nerve having severe NFI as defined above.

[b] Severe NFI = presence of any of the following: MRC grades 0, 1 for any motor nerve tested; or 3+ sensory point reduction for ulnar/median nerve distribution; or 5+ sensory point reduction for posterior tibial nerve distribution.

Table 4. Outcome of treatment of NFI by duration of NFI symptoms at 4 (A) and 12 (B) months

A

Duration of NFI	Nerve modality	Outcome at 4 months					Outcome at 4 months—proportions							
		Full	Partial	Same	Worse	Total	Full	*95% CI*	Partial	*95% CI*	Same	*95% CI*	Worse	*95% CI*
0–1 month	All sensory	28	37	7	10	82	0·34	*0·24–0·46*	0·45	*0·34–0·56*	0·09	*0·04–0·17*	0·12	*0·06–0·22*
	All motor	15	22	5	3	45	0·33	*0·20–0·49*	0·49	*0·34–0·64*	0·11	*0·04–0·25*	0·07	*0·02–0·19*
2–6 months	All sensory	29	22	24	2	77	0·38	*0·27–0·49*	0·29	*0·19–0·40*	0·31	*0·21–0·43*	0·03	*0·00–0·10*
	All motor	9	15	12	1	37	0·24	*0·12–0·42*	0·41	*0·25–0·58*	0·32	*0·09–0·26*	0·03	*0·00–0·16*

B

Duration of NFI	Nerve modality	Outcome at 12 months					Outcome at 12 months—proportions							
		Full	Partial	Same	Worse	Total	Full	*95% CI*	Partial	*95% CI*	Same	*95% CI*	Worse	*95% CI*
0–1 month	All sensory	29	30	12	18	89	0·33	*0·23–0·43*	0·34	*0·24–0·45*	0·13	*0·07–0·23*	0·20	*0·13–0·30*
	All motor	18	15	8	5	46	0·39	*0·25–0·55*	0·33	*0·20–0·48*	0·17	*0·08–0·32*	0·11	*0·04–0·24*
2–6 months	All sensory	33	21	19	4	77	0·43	*0·32–0·55*	0·27	*0·18–0·39*	0·25	*0·16–0·36*	0·05	*0·02–0·13*
	All motor	9	14	10	4	37	0·24	*0·12–0·42*	0·38	*0·23–0·55*	0·27	*0·14–0·44*	0·11	*0·04–0·26*

that 61% of patients with sensory loss and 49% of patients with motor loss showed some recovery.[5] This study also showed how the improvement is sustained at a year's follow-up, as it was in the present study. Kiran and others found that 74% of nerves showed 'marked improvement'.[2] In their review article, Rose and Waters reported that 75% of patients with loss of nerve function showed some, or a good recovery.[15] At the same project, Becx-Bleumink and Berhe reported that 88% of patients with acute nerve function loss regained complete or partial recovery of nerve function.[3] However, Lockwood and others found that only 50% of patients with neuritis in Hyderabad had some neurological improvement.[16] In Indonesia, Bernink and Voskens found that 75–80% of impaired nerves recovered partially or fully, using a standard prednisolone course of a minimum of 10 weeks.[17] Van Brakel found that nerve function improved in 30–84% of 186 patients (depending on the type of nerve). Schreuder in Thailand found that 83% of patients without impairments at the start of MDT and who developed NFI during treatment improved partially or completely with prednisolone.[18] Sugumaran in India found that 67% of paralysed ulnar nerves, 86% of median nerve paralyses and 78% of foot drops had partial or full recovery. His patients had more severe impairment of function than those in other studies, and he used long courses of corticosteroids (8–10 months).[19] A recent study in China using a standardized outpatient regimen reported that sensory NFI responded well with a recovery rate of 73·8, 76·5 and 81·0% in the ulnar, median and posterior tibial nerves, respectively. Recovery of motor function was much less satisfactory.[6]

The present study did not find convincing differences in the responses of different nerves, although there is a suggestion that for sensory function, the ulnar nerve responds best (77% improved at 12 months, versus 64% improvement for posterior tibial and 71% for median); and that for motor function the facial nerve recovers best (84% at 12 months), and the lateral popliteal recovers least well (47% improved at 12 months, versus 68% ulnar and 70% median). However, the 95% CIs (not given) are very wide. Other studies have reported different findings. Several studies report that median nerve sensory and motor function respond more readily than does ulnar.[2,3,6,19–21] The facial nerve is also reported as responding well with 70–75% of nerves recovering in two studies.[3,22] However, Van Brakel reported a much reduced recovery rate of 30%. Jiang reports good recovery of the posterior tibial nerve.[6] Taken together, the picture is variable and it may be summarized as broadly showing that there is an overall level of improvement of approximately 60-80% in impaired nerves following corticosteroid therapy.

The untreated group showed some rather surprising levels of recovery. By 12 months, 33% (19–51) of the function of untreated motor nerves had improved, with 9% (2–25) showing full recovery at 12 months [versus 33% (23–44) with full recovery amongst the treated group]. This proportion had risen from 20% (8–39) at 4 months. Spontaneous sensory recovery appears to be quite considerable, with 62% (50–73) showing some improvement at 12 months, and 17% (10–29) showing full recovery [versus 37% (30–45) with full recovery amongst the treated group]. The lower level of full recovery amongst the untreated group may reflect to some extent the greater severity of impairment—farther from which they had to recover.

Despite the selection bias in the untreated group and the obvious bias towards severity and short duration of symptoms, there is clearly a considerable spontaneous level of recovery, against which background the effectiveness of prednisolone must be set. It is unfortunate that the day has long passed when it would be ethical to conduct a randomized controlled trial to establish the true effectiveness of corticosteroids in the treatment of NFI.

The BANDS database was set up to record the duration of the *most recent* NFI present at registration only without recording the length of time more chronic, 'background' NFI was present. During analysis, it became clear that this was something of a design fault, since it has not been possible to determine how many patients had NFI present before the 'treatment episode' that this paper has studied. This has the effect of diluting some of the improvements noted, since chronic impairment may be expected to recover less than more acute NFI.

SEVERITY OF IMPAIRMENT AS AN OUTCOME INDICATOR

Two studies have reported that the level of impairment at the start of therapy has a bearing on the outcome. Van Brakel found that only 35% of patients with complete sensory NFI and 11% with motor paralysis improved to good function, compared with 67% and 55% respectively for patients with moderate impairment.[8] Srinivasan made a similar finding.[21] The present study, however, found little to substantiate this. A slightly higher proportion of sensory nerves from the *severely* affected group recovered than from the mildly affected group [70% (61–78) versus 63% (46–77)], although this was not statistically significant. Amongst motor nerves there was little difference, 69% (50–83) of the mildly impaired nerves showed some improvement, compared with 67% (52–79) amongst the more severely affected nerves. For both sensory and motor nerves, a higher proportion showed full recovery amongst the mildly affected group, although again this did not reach significance at the 5% level.

Whilst not all of the findings of other authors could not be corroborated from this study, the current study does show that it is possible for some nerves with more severe impairment to recover to full function.

DURATION OF IMPAIRMENT AS AN OUTCOME INDICATOR

It is generally thought that the more acute the NFI, the better the response to treatment.[15] Jiang's study shows that patients with sensory NFI with a duration of less than 1 month respond better than patients whose sensory NFI is of longer duration.[6] However, as in the case of severity of impairment as an indicator, this finding could not be substantiated, with relatively little difference in outcome at 12 months between the two groups, one with NFI duration of 0–1 month and the other of 2–6 months.

EHF IMPAIRMENT SCORES

The EHF impairment score of 0–12 has been used to give a more accurate picture of impairment than the standard WHO 0–2 disability grading system amongst leprosy patients, by assigning a WHO disability grade to each limb and eye, and summing the results for a total score. This method is rather different from the method already used. There is evidence that the EHF score does provide a fair indication of the impairment experienced by an individual.[23] In this respect, the changes detected in mean and median EHF scores probably represent a more realistic improvement for the patient himself. Motor NFI will register in the EHF scoring system only if there is a visible deformity (i.e. MRC grade ≤ 2 or lagophthalmos); whilst a WHO score of 1 for sensory NFI in a limb may indicate a small patch of anaesthesia or a loss of sensation in the entire limb. Further, it gives a level of impairment for a *patient;* the other method used in this study refers to *nerves.* However, it may be expected to at least parallel the findings discussed so far. In this respect, it gives

a clear indication that prednisolone treatment is effective, since there is a statistically significant ($P < 0{\cdot}001$) improvement in average EHF score from $2{\cdot}02 \pm 0{\cdot}21$ at the start of therapy to $1{\cdot}19 \pm 0{\cdot}21$ at 4 months, rising slightly to $1{\cdot}33 \pm 0{\cdot}27$ at 12 months, an overall improvement of 34%. The median score similarly improved from 2 to 1, confirming this finding. The average EHF score amongst the untreated patients at the start of treatment was $2{\cdot}32 \pm 0{\cdot}22$, confirming the earlier finding that the nerves in the untreated group were more severely impaired, and thus underlining the heterogeneity of the two groups. However, the mean EHF score for this group, whilst recovering, improved much less than in the treated group (to $2{\cdot}13 \pm 0{\cdot}25$ at 12 months), and the change was not significant at the 5% level. In addition, the median score did not change from 2.

UNTREATED GROUP

The discovery of a group of patients with acute NFI who should have received prednisolone therapy but did not is a significant finding in its own right. In all, 34% of the total number of patients needing prednisolone treatment for NFI did not receive it. This proportion of patients is an important indicator of a programme's effectiveness in the prevention of disability, and reasons for a high proportion of 'unjustly untreated' patients should be considered carefully.

The untreated group matched the treated group well in this study for sex, age and leprosy group. However there were distinct differences in terms of duration and severity of NFI, with a statistically significant bias towards more severe and acute impairment in the *untreated* group. This was perhaps the opposite of what was expected, that is, that mildly impaired patients with longstanding NFI would be missed. However, since the severity score is an absolute, and not a relative measure, this means that patients with longstanding NFI present before an acute episode and who then develop an acute episode, i.e. deteriorate further, will fall into the 'severe' category. Some of the missed patients therefore developed new NFI against a background of chronic impairment and this may explain in part why they were overlooked. Another important finding in this group was that many of them had a gradual decline in NFI over several months, rather than a sudden step-down in NF scoring. The field staff tended to look back to the records of the last month or two in assessing deterioration and thus missed NF loss spread out over several months. In addition, recovery followed by new, significant loss seemed to catch staff out.

The finding of spontaneous recovery amongst the 'unjustly untreated' group should be carefully interpreted. The levels of full recovery were much lower than among the treated group, and it is this which parallels the insignificant change in mean and median EHF scores which occurred amongst the untreated group of patients, since it takes full recovery for a patient to shift his WHO disability grade for a particular limb or eye. It is perhaps best to conclude that while there is evidence of spontaneous recovery, for most patients this may not amount to much.

Further examination of the 'unjustly untreated' group revealed that the clinical picture of leprosy and NFI was complicated by other disease entities (e.g. stroke) in nine cases. The clinical judgement of the field staff not to treat these patients according to the guidelines is respected, and may not necessarily have been incorrect.

LIMITATIONS OF PREDNISOLONE THERAPY

Despite prednisolone's effectiveness in treating acute NFI, there remains a core of patients who are resistant to its effects. As an overall figure, 32% (26–38) of all impaired nerves

were the same or worse at 12 months, despite prednisolone therapy; in 12% (9–17) nerve function had deteriorated. All these cases were treated with prednisolone in adequate doses within 6 months, the generally accepted treatment period for prednisolone treatment. Prednisolone has its limitations, and the authors agree with Van Brakel that it is important to search actively for more effective treatment for NFI.[8] Currently, ILEP is funding pilot studies on the use of azathioprine and cyclosporin in the treatment of type 1 reactions.

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The age-dependent deterioration in light touch sensation on the plantar aspect of the foot in a rural community in India: implications when screening for sensory impairment

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Summary Regular testing for impaired sensation is important in the management of diseases that can cause progressive nerve damage, such as leprosy. It has been shown that light touch sensibility decreases with age in the hands of healthy individuals, but little research has been undertaken to assess possible changes in the feet in developing countries. This information is needed to allow an appropriate level of sensation to be chosen when screening for nerve damage in the foot. To clarify this, a cross-sectional study on male adults was carried out in the rural town of Salur, Andhra Pradesh, India. A range of Semmes–Weinstein monofilaments were employed at 12 locations on the foot to determine sensation to light touch stimuli in individuals from each decade of adult life. It was found that in this population, sensibility threshold in the foot increases with age and this was noted in both soft and callous skin. This shows the increase was due to neurological factors, not merely due to an increase in callous deposition with advancing age. In the majority of individuals in their fifties and sixties, the callous skin at the forefoot and heel was unable to detect the 5.07 monofilament (equivalent to 8–12 g), previously recommended as a method to screen for plantar neuropathy. All areas of all feet were able to detect the 5.46 filament (approximately 30 g). The size of this study (54 individuals) prevents the determination of definitive normal ranges for each decade of life in this population. However, it does demonstrate the degree to which sensation deteriorates with age and could be used as an approximate guide when interpreting the results of sensory testing in similar rural areas of the developing world.

Introduction

The feet of leprosy patients are prone to sensory impairment following lesions of peripheral nerves. Often neuropathy persists after microbiological cure and the challenge of prevention of complications can remain throughout life. Complications in the foot include resorption of

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the toes, paralysis of the intrinsic muscles of the foot, cracks and fissures in excessively keratinized skin, ulceration on the plantar surface of the foot, osteomyelitis and malignancy.[1] In consequence, screening programmes have been established in leprosy control programmes so that nerve damage is identified as early as possible. Sensory testing is used both in the diagnosis of leprosy and also for monitoring patients to prevent new nerve damage from occurring. Any screening tool must be able to distinguish those with normal sensation from those with impaired nerve function at all ages. Without knowing what is normal, the recommendation of a screening tool to identify the abnormal is difficult.

The effect of ageing on light touch sensibility in the developing world requires clarification. Studies in developed countries have found that touch sensibility in the big toe deteriorates with advancing age,[2] and similar changes have been noted in the hands.[3,4] Two studies have briefly mentioned variation in sensibility with age in developing countries and have confirmed sensory deterioration with advancing age; sensation thresholds also appear to be higher than in more developed countries.[5,6] However, it is not clear if sensation of the soft skin of the toes and arch deteriorates in the same way as callous skin, so it is not known if the change is secondary to the build up of callous with age or deterioration in neurological function. Nor has the deterioration in sensation with age been discussed with regards to choosing a filament for screening purposes.

Graded monofilaments have been shown to be a sensitive, reproducible and practical method for both diagnostic screening for nerve damage and monitoring of sensation in the foot.[7–9] Our aim was to use these monofilaments to assess any change in light touch sensibility in the foot with increasing age. For this study, monofilaments of filament index 4.56, 5.07 and 5.46 were used. They are classically described as applying a force to the skin equivalent to roughly 4, 10 and 30 g.[10,11]

Materials and methods

Fifty-four healthy male individuals from the rural town of Salur in Andhra Pradesh State, India were asked to take part in the study and all agreed. They were not selected in a completely random manner, but were matched for age, occupation and footwear type with the cohort of male leprosy patients released from treatment from the town leprosy hospital between 1983 and 1988. This was to facilitate later research on these patients by using the findings of this study as a control. All of the individuals under study were without evidence of neurological disease. Since few participants knew their age more accurately than to the nearest decade, they were grouped in 10-year age bands. Only men were assessed, to minimize any variation in daily activity, and so foot stresses, associated with the differing roles of men and women in this population. No participant had sufficiently heavy alcohol intake to cause neuropathy. In an area characterized by monsoon and dry seasons, it might be expected that plantar sensation would vary as the skin becomes softened in the wet months and slowly hardens afterwards. In consequence, a study on the same individuals might yield differing results depending on the season. Again, high temperatures and humidity are thought to alter the properties of the Semmes–Weinstein nylon monofilaments, so that they buckle more easily than in cooler, dryer climates, and exert less force.[10] This work was undertaken during the months of November and December, at the end of the monsoon, with high humidity and temperatures typically between 20 and 30°C.

The Semmes–Weinstein monofilaments were tested on a Sartorius L2200P top-loading

balance to confirm their accuracy. Each filament was tested five times by applying perpendicularly to the balance until bowing, using a technique described elsewhere and the mean force calculated. The diameters were also checked using a binocular light microscope linked by a video camera to an RGB software package and compared with past work. The filament index numbers ($\log_{10} \times$ force required to bow the filament in tenths of mg) were then confirmed by consulting past research.[10,11] The mean force exerted by the filament of index 4.56 was 3.1 g, by index 5.07, 8.0 g and by index 5.46, 29.5 g. It is well known that monofilaments do not exert exactly the same force in practice as recorded by any of the manufacturers, as they are not made to exacting standards,[13] to make them more affordable. Variation tends to become more obvious as the index numbers become larger, and so the filaments thicker. The values listed here are comparable with past studies of the forces exerted by these nylon monofilaments.[10,11] Here we refer to the monofilament by its index number rather than by an estimation of the force it exerts.

All the patients and controls were examined by the same clinician to avoid inter-observer variation. Sensory function was assessed at the five toes, immediately distal to the first, third and fifth metatarsal heads, in the midfoot laterally and at the arch medially, and lateral and medial points on the heel, making 12 locations in all. The tests, outlined in detail elsewhere,[10,11,14] took place in quiet surroundings and were explained to each participant who then looked away from his feet. Semmes–Weinstein monofilaments with index 4.56, 5.07 and 5.46 were applied to each of the 12 locations in a concealed and random manner. The lightest filament detected at each location was documented.

Results

A summary of the characteristics of the group with regard to age, class of occupation and footwear is shown in Table 1. The group was tested with the range of monofilaments to determine the normal sensation in this population. Light touch sensation was not statistically significantly different between the left and right feet, so data from just the right foot of each individual were used in the analysis. This data are summarized in Table 2.

Table 1. Summary of the study population with regard to age (a), occupation (b) and footwear (c) (n = 54)

a				
Age groups				
Age in years	30–39	40–49	50–59	60–69
No. in age range (%)	12 (22)	16 (30)	18 (33)	8 (15)
b				
Occupation				
Light work (e.g. in office/shop)	22%			
Heavy work (e.g. labourer/farmer)	78%			
c				
Use of footwear				
Use of footwear	None	Sandals	Shoes	
At work	15%	85%	0%	
At home	100%	0%	0%	

Table 2. Sensibility thresholds in each age group

Filament size	No. of individuals detecting each filament			
	30–39 ($n = 12$)	40–49 ($n = 16$)	50–59 ($n = 18$)	60–69 ($n = 8$)
Location 1				
4.56	7	5	2	0
5.07	2	7	9	3
5.46	3	4	7	5
Location 2				
4.56	9	11	9	0
5.07	2	5	7	6
5.46	1	0	2	2
Location 3				
4.56	9	11	9	0
5.07	2	5	7	6
5.46	1	0	2	2
Location 4				
4.56	9	11	9	0
5.07	2	5	6	6
5.46	1	0	3	2
Location 5				
4.56	9	11	9	0
5.07	2	5	4	6
5.46	1	0	5	2
Location 6				
4.56	3	4	2	0
5.07	4	6	6	1
5.46	5	6	10	7
Location 7				
4.56	5	4	2	0
5.07	3	8	4	1
5.46	4	4	12	7
Location 8				
4.56	5	4	2	0
5.07	3	7	4	1
5.46	4	5	12	7
Location 9				
4.56	10	12	10	1
5.07	2	4	3	5
5.46	0	0	3	2
Location 10				
4.56	4	3	0	0
5.07	3	4	5	0
5.46	5	9	13	8
Location 11				
4.56	1	0	0	0
5.07	4	5	1	0
5.46	7	11	17	8
Location 12				
4.56	0	0	0	0
5.07	4	5	1	0
5.46	8	11	17	8

Numbers in italics represent locations.
Callous skin is present at locations 1, 6, 7, 8, 10, 11 and 12.
Soft skin is present at locations 2, 3, 4, 5 and 9.

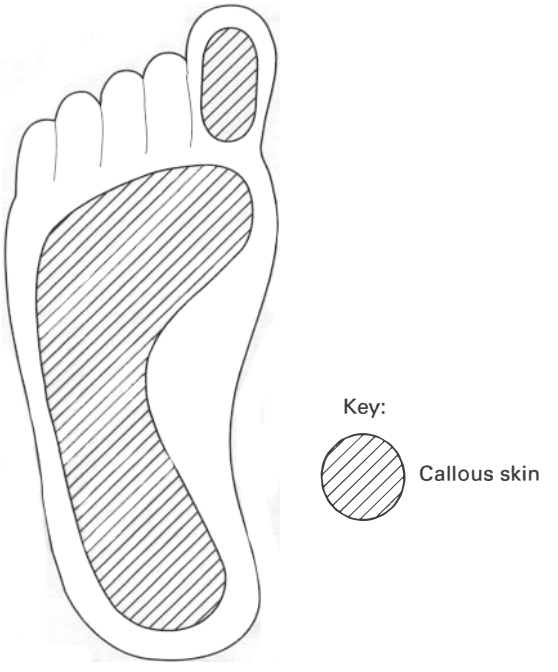

Figure 1. Distribution of callous skin on the plantar aspect of the foot.

To investigate the relationship between age and sensation threshold across all locations, a score out of 5 was given for soft skin (as there are five locations in areas of soft skin) and similarly out of seven for callous skin (Figure 1). For example, if subject A could feel the 4.56 filament as the lightest filament at locations 2, 3, 4 and 5, and the 5.07 filament at location 9, this would score 4 for the 4.56 filament, 1 for the 5.07 filament and 0 for the 5.46 filament. The use of this technique avoids inappropriately inflating the power of the tests by appearing to increase the number of individuals in the study by a factor of 12 (the number of locations). The Spearman's rho correlation coefficient was calculated for each filament across age groups. Detection of the 4.56 filament in both soft and callous skin was noted to decrease significantly with increasing age ($P = 0.001$). Detection of the 5.07 filament in soft skin also decreased significantly with age ($P = 0.019$) but there was no significant difference in callous skin. Conversely, there was a significant increase with age where only the 5.46 filament was detected, occurring in both soft ($P = 0.025$) and callous skin ($P = 0.001$). This relationship between age and sensibility threshold over all locations is shown in Figure 2. Examples of the relationship at the representative locations 1 (callous skin) and 9 (soft skin) is shown in Figure 3. Pearson chi-square test at individual locations also showed that there was a significant increase in sensory threshold with increasing age on comparing those in their thirties with those in their sixties (for example, $P = 0.037$ for location 1 and $P = 0.028$ for location 9).

A comparison between sensation at locations in soft skin areas and that in callous skin areas showed a significant difference between the groups. Analysis was performed using the Wilcoxon Signed Ranks test to compare the difference between soft and callous skin in each individual for the entire group. This demonstrated that soft skin had a lower sensation threshold than callous skin ($P < 0.001$).

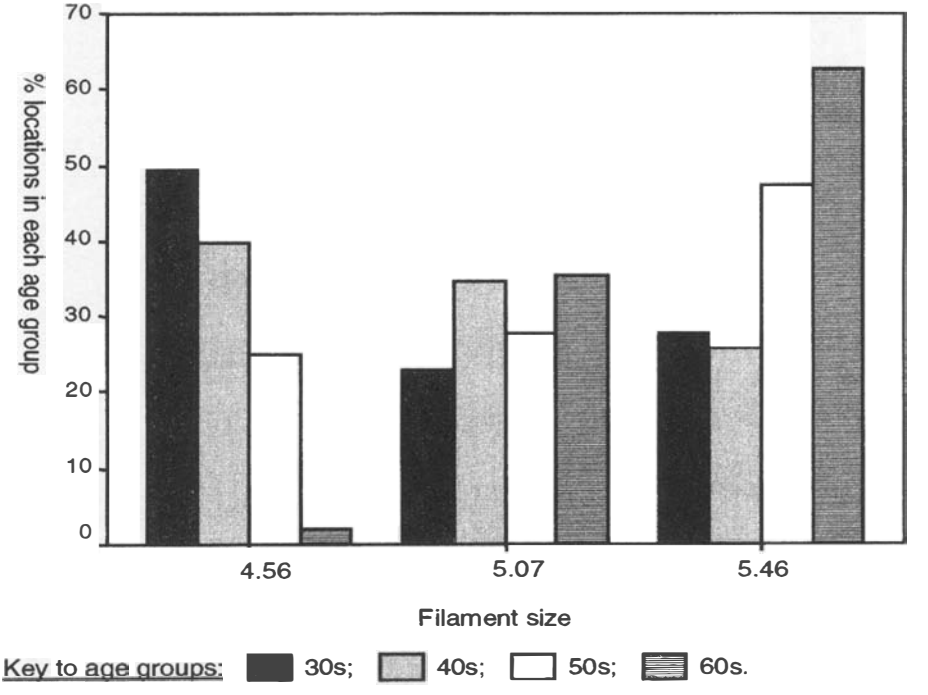

Figure 2. Graph showing the relationship between age and sensibility threshold to light touch at all locations.

A comparison between sensation in callous skin on the forefoot was compared with the heel, again using the Wilcoxon Signed Ranks test. The heel had a significantly higher sensory threshold in all age groups than the big toe ($P < 0.001$ in all age groups). These differences can be seen graphically in Figure 3, where sensibility threshold is shown for the callous skin at locations 1 and 12 and soft skin at location 9.

The final area of interest is the identification of the filament that can be detected by all individuals in all age groups at all locations on the foot. There were 648 locations in all on the right feet of the 54 individuals. Looking at all age groups combined, 31% of these locations detected the 4.56 filament, 30% were unable to detect this but could detect the 5.07 filament, while 39% detected only the 5.46 filament. Of particular note was that 81% of locations on the heel were only able to detect the 5.46 filament, nothing lighter. All locations in all feet were able to detect the 5.46 filament.

To summarize these results, firstly there is a clear and gradual deterioration in sensory acuity with age. Secondly, regardless of age, those areas covered with callus skin had a higher sensibility threshold than those covered with soft skin. Thirdly, the callous skin at the heel had a higher sensibility threshold than the callous skin of the forefoot. Finally, the callous skin at many locations was unable to detect any filament lighter than 5.46, most notably at the heel.

Discussion

In order to identify the abnormal, which is the purpose of screening, there has to be a clear

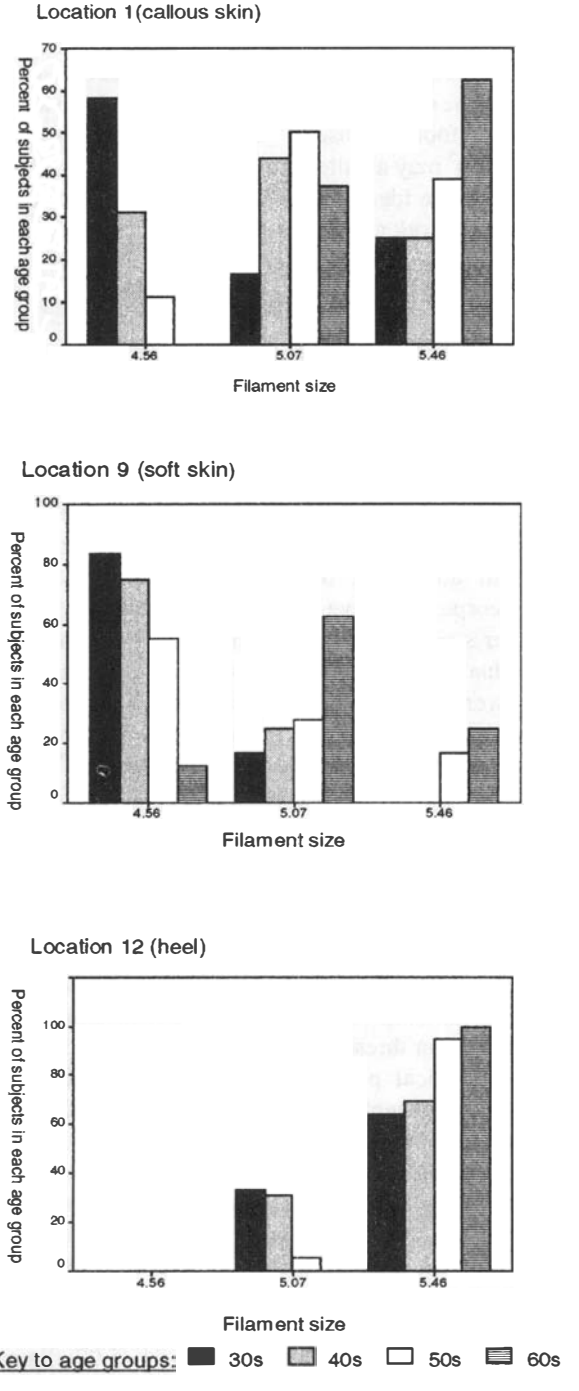

Figure 3. Graph showing the relationship between age and sensibility threshold to light touch at location 1 (callus skin), location 9 (soft skin) and location 12 (heel).

understanding of what is normal. A number of studies in developing countries have investigated normal sensation in the foot either as their primary aim,[6,15] or as a control group when testing sensation in leprosy patients.[9,16,17] Sensation might vary on the plantar aspect of the foot depending on a number of environmental factors, along with the number of years and individual lives to be exposed to these factors. It has been shown that environmental factors such as the type of footwear used,[17] the degree of hydration of the skin and the physical nature of occupation[5] may all alter light touch sensation. Genetic factors may also be important, as some studies have identified variation between men and women in older age groups,[2,18,19] although not all work confirms this.[20,21] Only a few studies have addressed the issue of the possible deterioration in light touch sensation in the foot with advancing age in a developing country.[5,6] While the deterioration with age has been noted, it has not been quantified or placed in context.

Sensory acuity in the skin of the limbs to light touch, pain and vibration is known to deteriorate with age.[4,18,20] Almost all studies have tested healthy individuals from the developed world, and the majority of work has investigated the hands, although a small number of studies have involved the big toe. The deterioration in sensation is more pronounced in the digits than proximally on the limb.[22] A combination of alteration in the mechanical properties of the skin and neural degeneration is thought to be responsible. Histological studies have found the distribution and morphology of touch-mediating receptors to change with advancing age. Meissner's corpuscles, Merkel cell neurite complexes and Pacinian corpuscles have all been implicated in this process. The reduction in the number of Meissner's corpuscles in the skin with ageing has been shown to be quite marked, so that an individual aged in his seventies will have lost around three-quarters of the receptors he had in his twenties.[21,23,24] Conduction along peripheral nerves and within the spinal cord is also slower in older persons.[25] In the central nervous system, the brain weighs less with old age, the cortex is thinned and the ventricles dilated.[26] All these changes help to explain how sensory thresholds in the skin of the hands and feet become elevated with advancing age.

The findings of this study show that there is a significant gradual loss of light touch sensation in the foot with advancing age in the poor rural south Asian population of Salur. This occurred at all sites tested on the foot, whether soft or callous skin. All previous studies of normal sensation in the developing world have been limited to callus skin and the potential advantages of testing soft areas have not been investigated. The closest equivalent has been the comparison between sensation in callus skin in those with shoes and those barefoot.[17] The finding that light touch sensation threshold increases with age on both soft and callous skin shows that this is a neurological phenomenon and not merely due to the build up of keratinized skin due to environmental factors. In our study, those aged in their thirties were usually able to detect the 4.56 filament on the soft skin of the toes and instep, while those in their sixties were typically unable to, usually detecting only the 5.07 filament. Findings for sensory threshold over callus areas are higher than the other developing world studies who tested a healthy group.[9,16,17] In our study, the lightest filament usually perceived on callus areas of the forefoot by those in their thirties and forties was the 5.07 filament, but by the fifties and sixties it was the 5.46. In all four age groups the lightest filament usually detected at the heel was the 5.46. No site anywhere on the foot in any age group was unable to detect the 5.46 filament. Results in previous work have been 4.31–5.07 filaments (2–10 g) on the forefoot and 4.56–5.07 (4–10 g) on the heel.[6,9,16,17] This is certainly related at least in part to their lower age range, with their mean ages similar to the very youngest in our study.

Furthermore, our sample contained a higher proportion of heavy manual workers than other studies. The variable environmental factors affecting the degree of callosity on the areas of the foot experiencing friction will mean that the differences between sensation in different populations will be most in callus skin and least in soft skin. Any screening tool is most useful if applicable to as many populations as possible. Therefore testing soft skin should be much more uniform between groups.

The finding that the 5.46 filament is the lightest felt by the majority at the heel in all adult age groups and in the forefoot in men aged in their fifties and sixties is of great importance. Past work to determine the threshold of protective sensation necessary to prevent neuropathic plantar ulceration has advised that the 5.07 filament be used.[9,27] It has been shown that skin able to detect this filament is highly unlikely to develop ulceration. However, work in Ethiopia found that many healthy individuals were failing this test, especially at the heel.[15] The study presented here has confirmed the finding in patients from a different continent, showing that it is not a local phenomenon. It is interesting that sensation at the heel is poorer than other parts of the foot still covered by callous skin. This may be related to possible variation in mechanical properties of the skin at different sites of the foot, or possibly to changes in the density of sensory receptors. In the hand it has been shown that while Pacinian corpuscles and Ruffini end organs are evenly distributed over the whole glabrous skin area, Meissner's corpuscles and Merkel cell neurite complexes are much less dense on the palm than the fingers.[28] While the receptors have not been studied in this detail in the foot, it is quite possible that a similar distribution would be found there too. If so, many normal individuals are failing the screening tests, especially those of older age groups; it is therefore possible that in some circumstances, a filament of higher index would be a more appropriate screening tool. In the rural population studied here, who either wore sandals or went barefoot and with a large proportion involved in heavy work, the 5.46 filament would be a suitable choice.

It is now clear that the age of an individual has a considerable effect on sensibility threshold in the foot. Increasing threshold is found with increasing age throughout adult life and this is not just a phenomenon in the elderly. This study illustrates the degree to which these changes effect light touch sensibility in a rural Indian community when tested with Semmes–Weinstein nylon monofilaments. The deterioration in sensation with age must be born in mind when testing the plantar aspect of the foot for nerve damage and therefore has great implications for the choice of monofilament by screening programmes.

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Mycobacterium w vaccine, a useful adjuvant to multidrug therapy in multibacillary leprosy: a report on hospital based immunotherapeutic clinical trials with a follow-up of 1–7 years after treatment

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Summary A vaccine based on autoclaved *Mycobacterium w* was administered, in addition to standard multidrug therapy (MDT), to 156 bacteriologically positive, lepromin negative multibacillary leprosy patients compared to a well matched control group of 145 patients with a similar type of disease who received a placebo injection in addition to MDT. The MDT was given for a minimum period of 2 years and continued until skin smear negativity, while the vaccine was given at 3-month intervals up to a maximum of eight doses. The fall in clinical scores and bacteriological indices was significantly more rapid in vaccinated patients, from 6 months onward until years 2 or 3 of therapy. However, no difference was observed in the fall in bacteriological index in the two groups from year 4 onwards. The number of LL and BL patients released from therapy (RFT) following attainment of skin smear negativity, after 24–29 months of treatment was 84/133 (63.1%) in vaccinated and 30/120 (25.0%) in the placebo group; the difference was highly statistically significant ($P < 0.0001$). In all, 90.2% patients (146/162) converted from lepromin negativity to positivity in the vaccine group, as against 37.9% (56/148) in the placebo group. The average duration of lepromin positivity maintained following eight doses

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of vaccine administered over 2 years was 3.016 years in the vaccine and 0.920 years in the placebo group. Histological upgrading after 2 years of treatment in the LL type was observed in 34/84 (40.5%) cases in the vaccine and 5/85 (5.9%) cases in the placebo group, the difference being statistically significant ($P < 0.001$). The incidence of type 1 reactions was significantly higher (30.5%) in the vaccine group than (19.7%) in the placebo group ($P = 0.0413$); the difference was mainly observed in LL type ($P = 0.009$). The incidence of type 2 reactions was similar (31.8 and 34.6%) in vaccine and placebo groups. The vaccine did not precipitate neuritis or impairments over and above that encountered with MDT alone. After 5 years of follow-up following RFT, no incidence of bacteriological or clinical relapses was observed in both groups.

Introduction

Vaccines have played a dominant role in control of infectious diseases and it should hold true for leprosy also. The multidrug therapy (MDT) regimes for leprosy recommended by the World Health Organization (WHO) in 1982 have been implemented globally, largely as a result of encouragement from WHO and interest and cooperation on the part of national governments. This new strategy of operation has brought an appreciable reduction in prevalence rate of the disease, which stood around 10–12 million at the beginning of the 1980s, with nearly 4 million cases from India. These figures came down to 0.95 million and 0.5 million cases, respectively, by 1996.[1,2] Multibacillary (MB) leprosy was treated for a minimum of 2 years or until skin smear negativity as per initial guidelines, later on the recommended treatment schedule was for a fixed duration of 24 months and recently this has been further reduced to 12 months. The 2-year regime for MB leprosy is now considered desirable only in cases with a high bacteriological index (BI) who either deteriorate or do not improve after 12 months of therapy.[3] Chemotherapy hardly affects cell mediated immunity (CMI) and hence the inherent immunological defect of MB patients is expected to continue even after complete bacteriological clearance.

The present approach of treating the MB cases with MDT of fixed duration leaves bacteriological clearance to the host CMI/macrophage system, which is already compromised in MB cases. However, this could be achieved by strengthening the host defence by other interventions such as an effective immunomodulator to hasten the bacterial clearance and clinical regression, and also inducing immuno-upgrading which would be more relevant with the short duration FDT. Skin smear positivity in MB cases is a concern, because the residual bacillary load puts the patient at risk of relapse and reactional episodes. Thus some form of immunomodulatory intervention along with chemotherapy may be desirable, whereby the patients could be rendered bacteriologically negative in a shorter time and the CMI status boosted to impart protection against reinfection.

The *Mw* vaccine, based on an atypical, saprophytic, cultivable, rapidly growing mycobacterium, has been under clinical trials at the urban leprosy centres of two major hospitals in Delhi, Safdarjung Hospital and Dr Ram Manohar Lohia Hospital, since 1987. The preliminary results of the study have been reported previously, though the follow-up was limited.[4–10] This communication reports the complete analysis of the cases from the time of induction into the study, to date with a follow-up period of varying durations (1–7 years) after release from treatment (RFT) following bacteriological negativity. At least 56 and 45% of

patients in the vaccine and placebo groups, respectively, have been followed up for more than 5 years for reactional states, impairments and relapses.

Materials and methods

VACCINE, PLACEBO AND LEPROMIN PREPARATIONS

The vaccine is a suspension of killed *Mycobacterium w* (*Mw*) in physiological saline in the concentration of 10^{10} bacilli per ml as reported earlier.[11] For plecebo, an autoclaved solution of micronized starch (Sarabhai Chemicals, Baroda, India) was used at a strength of 1 g per 100 ml distilled water, dispensed in sterile vials. For lepromin testing, armadillo-derived lepromin containing $30–40 \times 10^6$ killed bacilli per ml was kindly made available by IMMLEP/TDR of WHO (Lot No. C-1, Preparation date 06/14/89, NHDC, Carville, LA, USA).

VACCINE DOSE, REGIMEN AND ADMINISTRATION

The first dose of vaccine was 1×10^9 autoclaved bacilli in 0.1 ml physiological saline (0.85% NaCl). Subsequent doses contained half the number, i.e. 5×10^8 bacilli in 0.1 ml. The vaccine was administered intradermally in the deltoid region. In all, eight doses were given at 3-month intervals, over a period of 2 years.

MULTIDRUG THERAPY (MDT)

In the initial phase, MDT consisted of 2 weeks of intensive therapy with 600 mg rifampicin, 100 mg clofazimine and 100 mg dapsone daily. Subsequently, the patients received the WHO recommended regimen of 600 mg rifampicin and 300 mg clofazimine once a month, supervised, plus 100 mg dapsone and 50 mg clofazimine daily, self-administered.[12] The MDT was given for a minimum period of 2 years and continued thereafter until skin smear negativity was attained.

SUBJECTS AND STUDY DESIGN

Permission of the Drug Controller General of India, and Institutional Ethics Committee was obtained before initiating the study. Written consent of the subjects was taken before inducting them in the trial. The enrolled subjects comprised active, untreated MB leprosy patients belonging to LL, BL and BB forms. They were bacteriologically positive in slit-skin smear examination and lepromin negative, thus consisting of a suitable class of patients where the immunomodulatory effects of boosting of CMI responses by an immunomodulator could be critically assessed. The diagnosis was confirmed by clinical, bacteriological and histopathological examination of the skin lesions. The patients were allotted to the vaccine and placebo groups in a randomized manner as per the codes supplied by the statistician.[4] Standard MDT was administered to all cases; in addition, one group received the vaccine, whereas the other was given an injection of micronized starch (the identity of the injection was kept under code) as placebo.

The ongoing clinical trials had two series of cases. The first series (single blind) comprised 120 MB leprosy patients, where vaccine codes were known to the Head of the

clinic but not to the attending clinicians. The second (double blind) series of trial comprised 300 MB patients, in which neither the evaluating agency nor the attending clinicians were aware of the identity of the injection administered. To ensure blinding, the upper part of the arm, i.e. the vaccination/placebo site, was covered with a cloth napkin by the non-medical assistant before the patient was examined by the Medical Officer. The same procedure was adopted while recording the lepromin response. The slides for BI smears were prepared by paramedical staff in the clinic and were coded with index numbers that were subsequently read by the medical officer at NII, without any clue to the identity of the vaccine codes. The vaccine codes were opened in 1992 for analysis of the data, after which the data from both the series were combined, as the protocol followed for treatment and follow-up in the two series were similar and the parameters of monitoring were identical. However, for the follow-up in the clinics, the blinding procedures mentioned above were continued during clinical examinations even after decoding.

The effects of the vaccine were assessed using criteria of clinical scoring, BI, lepromin status and histopathological features.

CLINICAL SCORES

The clinical scoring was done by the attending physician and a record of these was maintained in the form of body charting done at 6-month intervals. For the purpose of clinical assessment, Ramu's clinical scoring method was followed, in which a score of 1–4 is given to lesions depending on their characteristics as depicted in Table 1. The body is divided into seven regions: (1) head and neck, (2) chest, abdomen and genitalia, (3) and (4) left and right upper limbs, (5) back and buttock, and finally (6) and (7) left and right lower limbs. Each region is scored independently from 1 to 4.[13,14]

In the initial part of the trial in the single blind series, the clinical scoring was done using the original Ramu's scoring system just described, where the maximum recordable score was 28. However, in the second phase, in order to make the scoring more qualitative, a modified system of clinical scoring was adopted in which each of the seven sectors of the body was further subdivided into four subsectors and given a score according to the clinical type of the lesion in each subsector. In this way there were $7 \times 4 = 28$ subsectors of the body and the maximum recordable score in the modified system was $28 \times 4 = 112$. The clinical details of the patients were recorded in clinical photographs taken at 6-month intervals.

BI

The skin-slit smear examinations for BI were carried out at 3-month intervals till the point of smear negativity, and thereafter at yearly intervals during follow-up. The smears were

Table 1. Ramus's system of clinical scoring

Score	Type of clinical lesions
1	Macules with minimal erythema and shiny infiltration
2	Well marked erythema and diffuse infiltration
3	Thick infiltration with flat topped papules and plaques
4	Infiltration with thick papulonodular lesions

collected from active lesions from six sites, stained using standard procedures and graded using the Ridley scale.

LEPROMIN AND HISTOPATHOLOGICAL EVALUATION

The lepromin status was assessed every 3 months during the first 2 years of therapy, and at 1-year intervals thereafter during the follow-up period. The histopathological monitoring comprised histopathological grading and classification. The tissue BI was carried out at 6-month intervals during immunochemotherapy.

REACTIONAL STATES AND NEURITIS

Type 1, type 2 reactions and neuritis were recognized by clinical features. A type 1 reaction was defined as visible changes in the skin lesions marked by prominence, erythematous hue and a subjective feeling of warmth, associated with or without constitutional symptoms. Type 2 reaction was defined as an episode of systemic illness with fever, aching, bony tenderness, joint pains with or without specific involvement of other organs such as eyes, kidneys, testis etc., also irrespective of appearance of characteristic lesions of erythema nodosum leprosum. An episode of neuritis was diagnosed on noticing thickened tender nerves in presence or absence of inflamed skin lesions. Peripheral nerves were examined for thickening and tenderness; superficial sensations (temperature, pain and touch) were tested using a temperature tester (supplied by WHO), pin and cotton wisp, respectively. Motor functions were assessed using voluntary muscle testing.[15] In all three types of complications, only those episodes were counted which required management with non-steroidal anti-inflammatory drugs, prednisolone, clofazimine, etc. A proforma sheet for leprosy reaction was filled in during each reactional episodes.

STATISTICAL ANALYSIS

The statistical analysis of the data on clinical scores and bacteriological indices was done using parametric tests, considering the observations for different time points. The comparison of decline between the vaccine and placebo groups has been done using two-sample *t*-test. The comparison of durations of lepromin positivity in the two groups has also been done using Student's *t*-test. The statistical significance of number of patients released from treatment (RFT) at various time periods, that of histopathological upgradation observed in patients from two groups, and the number of patients showing conversion to lepromin positivity, have been compared using the chi-square test.

Results

The initial status of patients were comparable in the vaccine and placebo groups in terms of clinical score, bacteriological indices, histopathological and lepromin status.

CHANGES IN BI

Table 2 shows the fall in BI over a 5-year period from initiation of MDT, including 2 years of

Table 2. Changes in bacteriological indices (BI)

Type of disease	Group (no. of cases)	Initial BI* [mean ± SE (*n*)]	Cumulative mean decline in BI by different time points [mean decline ± SE (*n*)]						
			6 months	1 year	18 months	2 years	3 years	4 years	5 years
LL	Vaccine (83)	3.77 ± 0.13 (83)	1.04 ± 0.14 (83)	1.50 ± 0.15 (83)	2.14 ± 0.14 (83)	2.68 ± 0.12 (83)	3.23 ± 0.09 (80)	3.44 ± 0.07 (65)	3.66 ± 0.06 (47)
	Placebo (81)	3.90 ± 0.12 (81)	0.51± 0.13 (81)	0.89± 0.12 (80)	1.25±0.13 (79)	1.74± 0.14 (79)	2.91± 0.11 (73)	3.44±0.09 (62)	3.73± 0.07 (42)
	Statistical significance	NS	$t = 2.72$ $P = 0.007$	$t = 3.08$ $P = 0.002$	$t = 4.47$ $P = <0.001$	$t = 4.90$ $P = <0.001$	$t = 2.05$ $P = 0.04$	$t = 0.04$ $P = 0.96$	$t = 0.72$ $P = 0.47$
BL	Vaccine (48)	2.37 ± 0.16 (48)	1.16 ± 0.14 (48)	1.60 ± 0.11 (48)	2.08 ± 0.06 (48)	2.15 ± 0.05 (48)	2.37 ± 0.01 (41)	2.37 ± 0.01 (29)	2.37 ± 0.01 (24)
	Placebo (41)	2.12 ± 0.19 (41)	0.47 ± 0.17 (41)	0.74 ± 0.15 (41)	1.12 ± 0.10 (41)	1.54 ± 0.09 (41)	1.83 ± 0.08 (41)	2.24 ± 0.03 (41)	2.24 ± 0.57 (41)
	Statistical significance	NS	$t = 3.04$ $P = 0.003$	$t = 4.36$ $P = <0.001$	$t = 7.54$ $P = <0.001$	$t = 5.78$ $P = <0.001$	$t = 8.09$ $P = <0.001$	NS	NS
BB	Vaccine (24)	0.58 ± 0.07 (24)	0.39 ± 0.04 (24)	0.52 ± 0.02 (24)	0.52 ± 0.02 (24)	0.52 ± 0.02 (24)	0.52 ± 0.02 (19)	0.52 ± 0.02 (14)	0.52 ± 0.02 (12)
	Placebo (23)	1.03 ± 0.20 (23)	0.45 ± 0.13 (23)	0.60 ± 0.13 (23)	0.73 ± 0.10 (23)	0.86 ± 0.06 (23)	0.95 ± 0.03 (20)	0.95 ± 0.03 (13)	0.95 ± 0.03 (9)
	Statistical significance	NS	t =0.46 $P = 0.64$	$t = 0.54$ $P = 0.58$	NS	NS	NS	NS	NS

*Initial BI = bacteriological index at the time of induction.
NS = not significant.

immunochemotherapy and 3 years of chemotherapy. Although about 50% of patients were followed up for over 5 years, the BI has been shown only for 5 years, since they became bacteriologically negative. No relapses were observed. Grouped according to the histological criteria, a significantly faster rate of BI decline was observed in the LL and BL vaccine groups from 6 months to 3 years, as compared to the placebo group; thereafter the difference in the two groups was non-significant. The majority of cases attained BI negativity in the vaccine group after 2 years of therapy, while the fall in BI in the placebo group occurred gradually and patients attained bacteriological negativity after 4–5 years of therapy. In BB type, the initial BI itself was very low and following therapy, no statistically significant difference was observed between the vaccine and placebo groups, at any stage of therapy.

CHANGES IN CLINICAL SCORES

Table 3 shows the mean values of clinical score (CS) at different time points over a period of 5 years from the commencement of therapy. Clinically, this was evident as regression and flattening of papulonodular lesions and plaques, and disappearance of hypopigmented lesions and diffuse infiltration. The statistically significant difference between the vaccine and placebo groups ($P < 0.001$) is observed in LL and BL leprosy after 2 years of therapy. In BB leprosy, however, the difference between the vaccine and placebo groups was not statistically significant at any stage of treatment.

CHANGES IN LEPROMIN STATUS

At induction, all patients were lepromin negative in their late (Mitsuda) response. With progressive immunization, there was a gradual increase in number of patients showing conversion to lepromin positivity. After 2 years of immunochemotherapy, 94.4% of LL patients converted to positivity in the vaccine group as compared to 7.3% in the placebo group. In BL leprosy, 64% of cases converted to positivity in vaccine as against 14.6% in the placebo group and in BB type, the corresponding figures were 94.4 and 53% for vaccine and placebo groups, respectively. The differences between vaccine and placebo groups, in respective leprosy types, were highly statistically significant ($P < 0.001$).[16]

Table 4 shows the durations for which lepromin positivity was sustained. The majority of the patients in both vaccine and placebo groups reverted back to lepromin negativity during late stages of follow-up. The average durations of positivity in LL, BL and BB types were 2.38, 2.22 and 4.45 years in the vaccine group, and 0.21, 0.65 and 1.90 years in the placebo group, respectively. The differences between vaccine and placebo groups were statistically significant in all three leprosy types. The overall duration of lepromin positivity in all three types of leprosy, taking into account the cases who did not convert to lepromin positivity at any stage, was calculated as 3.016 years in the vaccine group and 0.920 years in the placebo group.

RELEASE FROM TREATMENT

Patients were released from treatment (RFT) after three consecutive slit smears at monthly intervals were negative for acid fast bacilli (AFB). Figure 1 depicts the percentages of patients released from therapy at different ranges of therapy duration, after which they became skin smear negative. In LL type, 45.2% (38/84) patients attained skin smear

Table 3. Changes in clinical scores

Type of disease	Group (no. of cases)	Initial* [mean ± SE (*n*)]	Mean clinical scores at different time points [mean ± SE (*n*)]				
			1 year	2 year	3 year	4 year	5 year
LL	Vaccine (83)	52.6 ± 2.4 (83)	31.7 ± 2.1 (83)	17.0 ± 1.3 (83)	8.5 ± 1.0 (53)	4.2 ± 0.8 (38)	2.7 ± 0.6 (34)
	Placebo (81)	51.3 ± 2.2 (81)	33.6 ± 1.8 (80)	26.4 ± 2.1 (78)	14.6 ± 1.8 (45)	9.0 ± 1.45 (29)	4.17 ± 1.4 (29)
	Statistical significance	NS	$t = 0.67$ $P = 0.501$	$t = 3.80$ $P = <0.001$	$t = 2.92$ $P = 0.004$	$t = 2.85$ $P = 0.005$	$t = 0.90$ $P = 0.369$
BL	Vaccine (48)	41.9 ± 3.2 (48)	20.5 ± 1.8 (48)	9.0 ± 1.1 (47)	5.0 ± 1.3 (33)	0.87 ± 0.4 (17)	1.3 ± 0.8 (20)
	Placebo (41)	41.1 ± 3.2 (41)	22.6 ± 2.4 (41)	15.6 ± 1.8 (40)	11.3 ± 2.8 (18)	5.1 ± 1.6 (15)	0.6 ± 0.1 (21)
	Statistical significance	NS	$t = 0.70$ $P = 0.484$	$t = 3.09$ $P = 0.002$	$t = 2.02$ $P = 0.048$	$t = 2.38$ $P = 0.024$	$t = 0.18$ NS
BB	Vaccine (24)	34.7 ± 4.6	15.6 ± 3.2	9.2 ± 2.4	5.4 ± 2.8	3.9 ± 2.6	0.2 ± 0.2
	Placebo (23)	36.9 ± 3.6 (23)	21.7 ± 1.8 (23)	13.9 ± 2.3 (22)	9.7 ± 2.09 (12)	2.0 ± 1.0 (6)	0.6 ± 0.3 (10)
	Statistical significance	$t = 0.37$ NS	$t = 1.63$ $P = 0.109$	$t = 1.36$ $P = 0.179$	$t = 1.22$ NS	$t = 0.67$ $P = 0.512$	$t = 0.75$ $P = 0.46$

*Initial = clinical score index at the time of induction.
NS = not significant.

Table 4. Duration of lepromin positivity in varous groups

	Sustained long-term positivity (years) [mean ± SE (no. of cases)]		
Total cases	LL	BL	BB
Vaccine	2.38 ± 0.28 (62)	2.22 ± 0.31 (44)	4.45 ± 0.63 (22)
Placebo	0.21 ± 0.11 (76)	0.65 ± 0.29 (33)	1.90 (14)
Statistical significance	$P < 0.001$	$P = 0.001$	$P = 0.01$

Overall positivity in all three types of leprosy, i.e. LL, BL and BB following 8 doses of immunotherapy and chemotherapy: vaccine group: 3.016 years; placebo group: 0.920 years.

negativity after 24–29 months of therapy in the vaccine group, as against 20.2% (16/79) patients in placebo. In BL type the corresponding figures were 93.8% (46/49) for vaccine and 34.1% (14/41) for placebo group. Similarly, the figures in the BB type were 95.8% (23/24) and 78.2% (18/23), respectively.

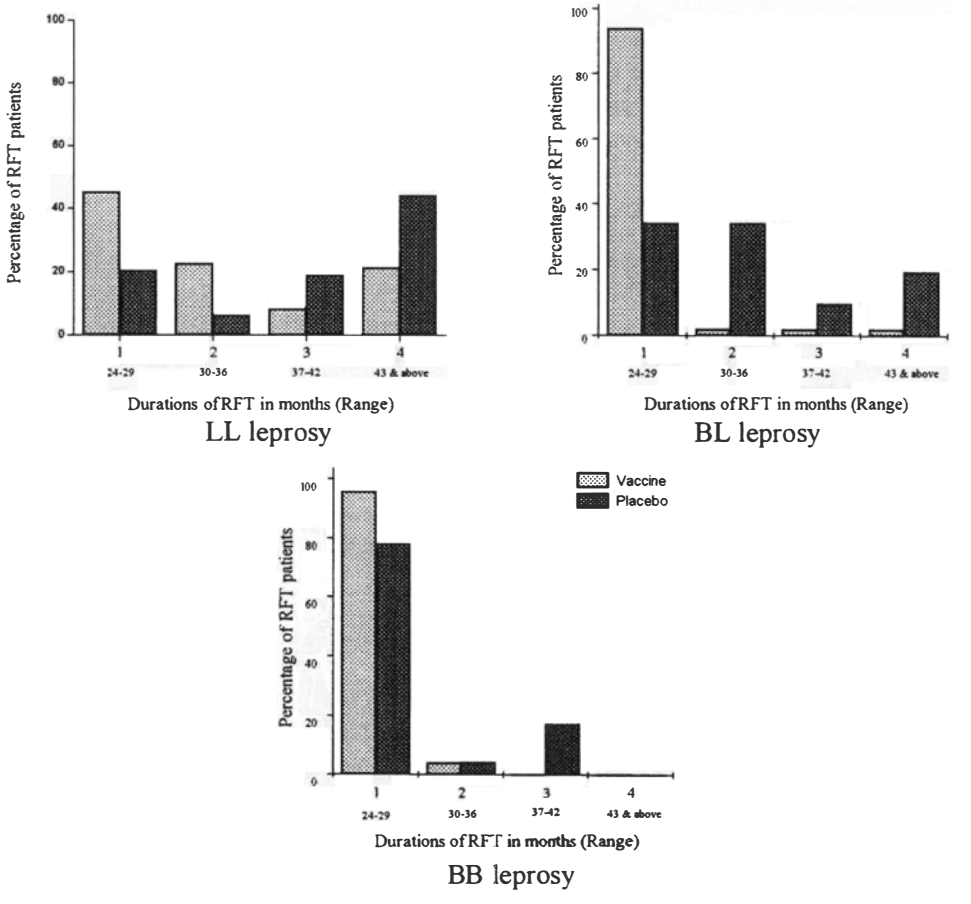

Figure 1. Percentages of patients released from treatment (RTF) following attainment of skin smear negativity in LL, BL and BB leprosy types in vaccine and placebo groups.

Table 5. Incidence of reactional episodes and neuritis

Group (304)	Type 1 reaction			Type 2 reaction			Neuritis		
	LL (84)	BL (49)	BB (24)	LL (84)	BL (49)	BB (24)	LL (84)	BL (49)	BB (24)
Vaccine (157)	25 (29.7%)	17 (34.6%)	6 (25.0%)	42 (50.0%)	7 (14.2%)	1 (4.1%)	31 (36.9%)	15 (30.6%)	5 (20.8%)
	48 patients (30.5%)			50 patients (31.8%)			51 patients (32.4%)		
Placebo (147)	LL (83)	BL (41)	BB (23)	LL (83)	BL (41)	BB (23)	LL (83)	BL (41)	BB (23)
	10 (12.0%)	10 (24.3%)	9 (39.1%)	43 (51.8%)	7 (17.1%)	1 (4.3%)	36 (43.3%)	12 (29.2%)	6 (26.1%)
	29 patients (19.7%)			51 patients (34.6%)			54 patients (36.7%)		
	$P = 0.0413$*			$P = 0.686$			$P = 0.510$		
P value	0.009	0.406	0.468	0.937	0.943	0.489	0.487	0.926	0.936

*The *P* values were calculated using chi-square. The value for type 1 reaction for all categories combined ($P = 0.0413$), after Bonferroni's correction becomes $P = 0.124$. The significance for the same figures calculated by Mantel–Haenszel chi-square test is $P = 0.137$. Power size calculation for BB type is 70% for type 1 reactions.

The overall number of cases attaining skin smear negativity after 24–29 months of treatment in LL and BL types of leprosy combined, was 84/133 (63.1%) and 30/120 (25.0%) in the vaccine and placebo groups, respectively, and the difference was highly significant statistically ($P < 0.0001$).

INCIDENCE OF REACTIONS AND NEURITIS

Table 5 presents the number of patients experiencing type 1, type 2 reactions and neuritis in the two groups. The numbers of such patients have been compared in total, as well as against the respective categories from vaccine and placebo groups. There is no statistically significant difference with respect to type 2 reactions and neuritis in any leprosy type. However, the incidence of type 1 reactions was higher in the vaccine group as a whole ($P = 0.041$, odds ratio 1.79), mainly because of higher incidence observed in LL leprosy, i.e. 25 patients out of 84 (29.7%) in vaccine group, as against 10 out of 83 (12.0%) in the placebo group; this difference is statistically significant ($P = 0.009$). However, the same difference was not significant after the *P* value was corrected for the number of variables, and also when calculated by multivariate analysis. The higher rate of type 1 reaction in the vaccine group was not associated with any rise in the rate of sensorimotor impairments; details are reported elsewhere.[17]

HISTOLOGICAL CHANGES

Histological monitoring was done through skin biopsies taken every 6 months from the same site. Histological improvement, i.e. histological upgrading and/or granuloma clearance, was seen in 34/84 (40.5%) of vaccinated LL patients at 24 months, as compared to 5/85 (5.9%) in control group ($P < 0.001$). Of these 34 cases showing histopathological upgrading in the vaccine group, 14 showed a complete disappearance of dermal granuloma giving a picture of non-specific infiltration (NSI) at the end of 24 months of treatment. This was more evocatively demonstrated in BL vaccinated patients, where 35 out of total 47 cases showed upgrading (74.5%) and 32 of those 35 (91.4%) showed NSI. The overall rates of

Table 6. Post-RFT follow-up of MB leprosy patients treated with MDT with/without *Mw* vaccine

Group (304)	5–10 years	2–5 years	1–2 years	<1 years	Not followed up	Average follow-up period*
Vaccine (157)	88 (56.0%)	38 (24.2%)	7 (4.4%)	8 (5.1%)	16 (10.2%)	5.60 years
Placebo (147)	66 (44.9%)	35 (23.8%)	9 (6.1%)	9 (6.1%)	28 (19.0%)	5.06 years

*Average follow-up period calculated excluding those not followed up.

histopathological improvement observed at 12 and 24 months demonstrate a statistically significant difference in the vaccine and placebo groups ($P < 0.001$).

Patients clinically classified as BB had varied initial histological features of indeterminate, BT, BT/BB or BB types. A follow-up of these patients for a period of 2 years did not reveal any appreciable differences in the two groups.

LOCAL REACTIONS TO VACCINE

The clinical experience of the trial has shown that the vaccine was well tolerated, without any major side effects. Local erythema and induration at the injection site, sometimes leading to ulcer formation, was the only problem observed in a few cases. These healed spontaneously in about a week's time.

POST-RFT FOLLOW-UP

Table 6 shows the number of patients that could be followed up after release from therapy for different durations. The average follow-up period was 5.60 years in vaccine and 5.06 years in the placebo group.

Discussion

Several candidate vaccines have been tested for their immunotherapeutic potential, viz. (i) killed *M. leprae* + BCG by Convitt *et al.*[18], (ii) Indian Cancer Research Centre strain (ICRC) by Bapat and Dev *et al.*[19] and (iii) *M. vaccae*, by Stanford *et al.*[20] However, the clinical trials with *Mw* are unique in several respects. These are the first trials where immunotherapeutic effects of an immunomodulator have been critically assessed in active multibacillary leprosy patients, by clinical, bacteriological, immunological and histological parameters.

Mw vaccine is based on an atypical, saprophytic, cultivable, rapidly growing mycobacterium. It resembles the bacilli included in Runyon's group IV, but differs in one respect or another from bacilli presently included in that group.[21,22] The recent studies based on nucleotide sequence in a polymorphic region of 65 kD gene indicate that *Mw* is a new species[23]. The basic research work of development of *Mw* vaccine began in the late 1970s and the background studies relating to its selection as a candidate anti-leprosy vaccine have been reported.[24–29] The phase I clinical trials were conducted in 1981 by Chaudhary *et al.* at Calcutta.[30]

Patients receiving *Mw* vaccine showed marked improvement in clinical features resulting in reduction of infiltration and rapid clearance of papulonodular lesions. As assessed through

Ramu's clinical scores,[13,14] vaccinated patients showed a statistically significant fall in scores in LL and BL types of leprosy after 2 years of therapy ($P < 0.001$). The BI decline in our study was faster among vaccinated patients; as many as 63.1% (84/133) BL and LL patients with high initial BI in the vaccine group attained bacteriological negativity within 24–29 months of treatment. The corresponding figure in the placebo group was 25.0% (30/120) and the difference was highly significant statistically ($P < 0.0001$). The histological improvement in the form of either upgrade or disappearance of granuloma was significantly more in vaccinated BL and LL patients ($P < 0.001$), as observed after 1 and 2 years of therapy. In both types together, 69 out of 131 (52.6%) showed histological upgrade, of which 46 (66.6%) showed a complete disappearance of dermal granuloma resulting in a histological picture of non-specific infiltration (NSI). In BB patients, histological upgrade was observed in both vaccine and control groups with little variation, which was not statistically significant.

Another beneficial effect of *Mw* vaccine as an immunotherapeutic supplement to MDT has been its impact on boosting the CMI of patients, as demonstrated by positive lepromin conversion. The duration of lepromin positive status in the cases receiving *Mw* vaccine was much longer as compared to those receiving the placebo. The overall duration of lepromin positivity in the vaccine and placebo groups, following administration of eight doses over a period of nearly 2 years, was 3.016 and 0.920 years, respectively. This gives some indication of the time period when a patient should receive a booster vaccination so as to keep them lepromin positive and prevent relapse or reinfection. A reasonable approach would be to administer a booster dose at an interval of 3 years after the patient has completed MDT.

The upgrade of CMI responses by the vaccine is also reflected by the higher incidence of type 1 reactions in vaccinated patients, notably in LL type. This was seen in 29.7% (25/84) patients in vaccine, as compared to 12% (10/83) in the control group. The number of patients experiencing type 2 reactions in the two groups did not show any statistically significant difference. Though not a parameter of the study, it was imperative to monitor incidence of reactions and impairments when using immunomodulators in leprosy. It was reassuring to note that for neuritis and deformities, *Mw* vaccine did not lead to any higher incidence over and above that observed with chemotherapy alone. This was also corroborated histopathologically, where vaccination did not precipitate inflammation of dermal nerve twigs.[6]

To sum up, the overall clinical, bacteriological and histological improvement amongst vaccinated patients was reflected by attainment of early skin-smear negativity and clinical inactivity, resulting in a shorter duration of effective treatment. Statistically significant number of LL and BL patients were released from treatment after 24–29 months of therapy ($P < 0.0001$), thus vaccinated patients had less morbidity, became BI negative faster. No case of clinical or bacteriological relapse was observed in the vaccine and placebo groups probably because MDT was continued till skin smear negativity in both the groups. The complete clearance of bacillary load could be a factor behind prevention of relapse/reinfection in the cases so far followed. It may be noted that in high initial BI cases, such a bacteriologically negative status is attained in the placebo group towards years 4 or 5 of chemotherapy while the similar status is attained in years 2 or 3 following immunochemotherapy as depicted in Figure 1. This shows that a significant number of patients with high BI (63.1% of LL and BL patients combined) could be rendered bacteriologically negative after 24–29 months of treatment. In other words, the results obtained with chemotherapy alone in 4–5 years could be achieved within 2–3 years following addition of immunotherapy with *Mw* vaccine to standard MDT as an adjunct.

The 7th WHO Expert Committee on Leprosy recommended on the basis of multicentric trials that it is possible to reduce the duration of the current WHO MDT regimen for MB leprosy, from 24 months to 12 months. The WHO Leprosy Elimination Advisory Group (LEAG) has, in its meeting on 16–17 July, 1997, endorsed the technical recommendation of the 7th Expert Committee and urged the national governments to implement the same. This communication intends to convey that in spite of visible changes in the disease scenario in the last decade, the relevance of immunotherapeutic intervention should not be undervalued and there are a number of problematic multibacillary leprosy cases (e.g. highly bacilliferous, slow or non-responsive MB cases) which can be dealt with successfully through this approach.

Acknowledgements

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Reactional states and neuritis in multibacillary leprosy patients following MDT with/without immunotherapy with *Mycobacterium w* anti-leprosy vaccine

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Summary A vaccine based on autoclaved *Mycobacterium w* was administered, in addition to standard multidrug therapy (MDT), to 157 untreated, bacteriologically positive, lepromin negative multibacillary leprosy patients, supported by a well matched control group of 147 patients with similar type of disease, who received a placebo injection in addition to MDT. The MDT was given for a minimum period of 2 years and continued until skin smear negativity, while the vaccine/placebo was given at 3-monthly intervals up to a maximum of eight doses. The incidence of type 2 reaction and neuritis during treatment and follow-up showed no statistically significant difference in the vaccine and placebo groups. The incidence of type 1 reaction (mild in most cases), however, was higher in the vaccine group ($P = 0.041$, relative risk ratio 1.79), considering LL, BL and BB leprosy types together, and considerably higher ($P = 0.009$) in LL type, probably because of confounding due to higher number of patients with previous history of reaction in this group. The occurrence of reactions and neuritis in terms of single or multiple episodes was similar in the vaccine and placebo groups. The association of neuritis and reactions, as well as their timing of occurrence (during MDT or follow-up), was also similar in the two groups, with more than 90% of occurrences taking place during MDT. The incidence of reversal reaction was significantly higher among the males in the vaccine group (34.5% versus 8.3%, $P = 0.019$). Patients with high initial BI (4.1–6.0) showed higher incidence of reactions (70.3%) as compared to those with medium (2.1–4.0) and low (0.3–2.0) BI where the reactions were observed with a frequency

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of 56.1% and 38.8%, respectively. However, unlike reactions, neuritis incidence did not seem to be affected by initial BI to the same extent in the vaccine group, with frequencies of 35.3%, 36.3% and 25.9% in the three mentioned BI ranges. Overall, the vaccine did not precipitate reactional states and neuritis over and above that observed with MDT alone.

Introduction

Reactional states and neuritis constitute an emergency in leprosy, calling for quick attention and proper management, since delayed or inadequate management of neuritis may lead to impairments which could become permanent. Two types of reactional states are well recognized, type 1 (reversal) reaction and type 2 reaction (erythema nodosum leprosum). Type 1 reactions, usually seen in borderline leprosy, occur most frequently during the initial phase of chemotherapy and are associated with abrupt rise in host cell mediated immune response to mycobacterial antigen.[1] Type 2 reaction (erythema nodosum leprosum) affects mainly multibacillary leprosy patients of LL and BL types. In one study, over 50% of LL and about 25% of BL patients experienced type 2 reaction;[2] in another study from South India an incidence of 35% of type 2 reactions has been reported in LL and BL patients.[3] The pathogenesis of this symptom complex is the formation of immune complexes which are deposited in various body sites; these complexes comprise mycobacterial antigens, IgG or IgM antibodies and complement.[4] The profile of reactions and neuritis presented in this communication forms a part of large scale clinical trials of a vaccine based on *Mycobacterium w* bacilli, under evaluation for its immunotherapeutic effects as an adjunct to multidrug therapy (MDT), in the hospital-based trial in Delhi since 1987.

Materials and methods

VACCINE

The vaccine is a suspension of killed *Mycobacterium w* in physiological saline in the concentration of 10^{10} bacilli per ml (the details of the vaccine preparation have been reported).[5] The first dose comprised 1×10^{9} autoclaved bacilli in 0.1 ml. physiological saline (0.85% NaCl) while subsequent doses contained half the number of bacilli, i.e. 5×10^{8}. The vaccine was administered intradermally in the deltoid region using a 30G needle. A total of eight doses were given at 3-month intervals, over a period of nearly 2 years.

PLACEBO

One gram of micronized starch (Sarabhai Chemicals, Baroda, India) was dissolved in 100 ml of distilled water, autoclaved at 15 lb per inch pressure for 15 min and dispensed in sterile vials.

MULTIDRUG THERAPY (MDT)

In the initial phase MDT consisted of 2 weeks of intensive therapy with 600 mg of rifampicin, 100 mg clofazimine and 100 mg dapsone daily. Subsequently, the patients received the WHO

recommended regimen of 600 mg rifampicin and 300 mg clofazimine once a month, supervised, plus 100 mg of dapsone and 50 mg clofazimine daily, self-administered. The MDT was given for a minimum period of 2 years and continued thereafter till the skin smear negativity was attained.

SUBJECTS AND STUDY DESIGN

Permission of the Drug Controller General of India and Institutional Ethics Committee was obtained before initiating the study. Written consent from the subjects was obtained before inducting them in the trial. The enrolled subjects comprised of untreated, lepromin negative, bacteriologically positive, active cases of multibacillary leprosy belonging to LL, BL and BB types. The diagnosis was confirmed on the basis of clinical examination and histopathology. The patients were allotted to the vaccine and placebo groups in a randomized manner as per codes supplied by the statistician.[5] The clinical trials had two series. The initial series comprising 120 patients of multibacillary (MB) patients was single blind, where the vaccine codes were known to the Head of the clinic but not to the attending clinician. The second series of trials, comprising 300 multibacillary patients, was double blind, in which neither the evaluating agency nor the patients were aware of the identity of the injection administered. The vaccine codes were decoded in 1992. In this report, the data from both the series have been combined as the protocol followed for treatment and follow-up in the two series was similar and the parameters of monitoring were identical. The average period of observation (including MDT and post-MDT follow-up) for the patients was 8.48 and 8.63 years in the vaccine and placebo groups, respectively.

REACTIONAL STATES AND NEURITIS

The type 1, type 2 reactions and neuritis were recognized based on clinical features. An episode of type 1 reaction was considered on noting visible changes in the skin lesions marked by prominence, erythematous hue and a subjective feeling of warmth, associated with or without constitutional symptoms. Type 2 reaction was considered as an episode of systemic syndrome with fever, aches, bony tenderness, joint pains with or without specific involvement of any organ, e.g. eyes, kidneys, testis, also irrespective of appearance of characteristic lesions of erythema nodosum leprosum. An episode of neuritis was diagnosed on observing thickened tender nerves in the presence or absence of inflamed skin lesions. Peripheral nerves were examined for thickening and tenderness, superficial sensations (temperature, pain and touch) were tested using a temperature tester (supplied by WHO), pin and cotton wisp, respectively. Motor functions were assessed using voluntary muscle testing.[6]

In all three types of complications mentioned, only those episodes were considered for counting which required management with non-steroidal anti-inflammatory drugs, e.g. prednisolone, clofazimine. A proforma for leprosy reactions was filled in at the time of the patient's induction and subsequently during each reactional episode. The details of present and past history of reactional and neuritis episodes, presence or absence of constitutional symptoms like fever, malaise, pain or tenderness of peripheral nerves, joint or muscle pain, development of sensory or motor deformities were recorded. The knowledge of past history of reaction was obtained from the patients and/or previous clinical records, whenever available. The patients were asked whether they had ever experienced the symptoms

Table 1. Incidence of reactional episodes and neuritis

Group (304)	Type 1 reaction			Type 2 reaction			Neuritis		
	LL (84)	BL (49)	BB (24)	LL (84)	BL (49)	BB (24)	LL (84)	BL (49)	BB (24)
Vaccine (157)	25 (29.7%)	17 (34.6%)	6 (25.0%)	42 (50.0%)	7 (14.2%)	1 (4.1%)	31 (36.9%)	15 (30.6%)	5 (20.8%)
	48 patients (30.5%)			50 patients (31.8%)			51 patients (32.4%)		
Placebo (147)	LL (83)	BL (41)	BB (23)	LL (83)	BL (41)	BB (23)	LL (83)	BL (41)	BB (23)
	10 (12.0%)	10 (24.3%)	9 (39.1%)	43 (51.8%)	7 (17.1%)	1 (4.3%)	36 (43.3%)	12 (29.2%)	6 (26.1%)
	29 patients (19.7%) $P = 0.0413$*			51 patients (34.6%) $P = 0.686$			54 patients (36.7%) $P = 0.510$		
P value	0.009	0.406	0.468	0.937	0.943	0.489	0.487	0.926	0.936

*The *P* values were calculated using chi-square. The value for type 1 reaction for all categories combined ($P = 0.0413$), after Bonferroni's correction becomes $P = 0.124$. The significance for the same figures calculated by Mantel–Haenszel chi-square test is $P = 0.137$. Power size calculation for BB type is 70% for type 1 reactions.

(characteristic of reactions/neuritis). Based on their responses/clinical records, it was deduced whether they had a previous history of reaction or not. Cases with mild reaction were managed with rest, physiotherapy and non-steroidal anti-inflammatory drugs (NSAID) for a period of 6 weeks, severe cases were managed with initial hospitalization, physiotherapy, oral steroids for a period of 12–20 weeks (along with NSAID, only if necessary, to avoid any possible gastrointestinal damage). The patients given steroids with NSAID were monitored closely.

STATISTICAL ANALYSIS

The comparative statistical analysis of reactional and neuritis episodes in the vaccine and placebo groups has been done using chi-square test. Incidence of reactions and neuritis, in cases stratified by the previous history of occurrence, has been analysed by Mantel–Haenszel test. The impact of initial BI on reaction and neuritis incidence has been analysed using chi-square test for trend. A P value of <0.05 was considered as significant.

Results

Table 1 presents the number of patients in vaccine and placebo group, under three leprosy types LL, BL and BB, experiencing type 1, type 2 reactions and neuritis. The numbers of these patients have been compared in total, as well as against the respective categories from vaccine and placebo groups. There is no statistically significant difference with respect to type 2 reactions and neuritis in any leprosy type. The incidence of type 1 reactions was higher in the vaccine group as a whole ($P = 0.041$, relative risk ratio 1.79); however, the difference did not remain significant ($P = 0.124$) on correction of P value for number of variables. The higher incidence of type 1 reaction in the vaccine group can be attributed to the higher incidence in LL leprosy, i.e. 25 patients out of 84 (29.7%) in the vaccine group, as against 10 out of 83 (12.0%) in the placebo group. This difference is statistically significant ($P = 0.009$). However, this is to be stated that nine out of 25 (36%) patients in the vaccine group and two out of 10 (20%) in the placebo group had a previous history of reaction and this difference was statistically significant ($P = 0.008$, data not shown in table).

Table 2 presents the occurrence of type 1 reaction, type 2 reaction and neuritis, with respect to single or multiple episodes in patients from the vaccine and placebo groups. It is seen that the single as well as multiple episodes of type 1 reaction occurred almost in equal percentages of patients in both groups, 62.5% in vaccine and 62.1% in placebo group for single episode, and 37.5% and 37.9%, respectively, for multiple episodes. Similarly, among the patients experiencing type 2 reaction and neuritis, no statistically significant differences were observed between the two groups during treatment and follow-up.

Table 3 shows the occurrence of neuritis and reactions in patients, taking place in association or in isolation. The number of patients remaining free from any neuritis or reactional state are nearly equal in vaccine and placebo groups, i.e. 36.9% and 36.7%, respectively. Similarly the number of patients experiencing only reactions, only neuritis and those experiencing both these, also show no statistically significant difference between the two groups.

Tables 4a and b depict the impact of previous history of reaction and neuritis, respectively, on their occurrence during treatment and post-treatment follow-up. The patients

Table 2. Incidence of reactional episodes and neuritis in terms of single or multiple episodes

Leprosy type (*n*)	Type 1 reaction (no. of patients)			Type 2 reaction (no. of patients)			Neuritis (no. of patients)		
	Total	Single episode	Multiple episodes	Total	Single episode	Multiple episodes	Total	Single episode	Multiple episodes
LL (V) (84)	25	12 (48.0%)	13 (52.0%)	42	20 (47.6%)	22 (52.4%)	31	17 (54.9%)	14 (45.1%)
BL (V) (49)	17	13 (76.5%)	4 (23.5%)	7	3 (42.8%)	4 (57.1%)	15	5 (33.3%)	10 (66.6%)
BB (V) (24)	6	5 (83.3%)	1 (16.6%)	1	1	–	5	4 (80.0%)	1 (20.0%)
Total (157)	48	30 (62.5%)	18 (37.5%)	50	24 (48.0%)	26 (52.0%)	51	26 (50.9%)	25 (49.1%)
LL (P) (83)	10	5 (50%)	5 (50%)	43	17 (39.5%)	26 (60.5%)	36	12 (33.3%)	24 (66.6%)
BL(P) (41)	10	4 (40%)	6 (60%)	7	3 (42.9%)	4 (57.1%)	12	7 (58.3%)	5 (41.7%)
BB(P) (23)	9	9	–	1	1	–	6	6	–
Total (147)	29	18 (62.1%)	11 (37.9%) $P = 0.857$	51	21 (41.2%)	30 (58.8%) $P = 0.887$	54	25 (46.3%)	29 (53.7%) $P = 0.939$

P values indicate the statistical comparison between vaccine and placebo groups for type 1, type 2 reactions and neuritis. Analysis was done by Mantel–Haenszel chi-square test.

Table 3. Incidence of reaction and neuritis occurring in isolation or in combination

Group	No.	No. Rxn/neuritis	Only reaction	Only neuritis	Both Rxn and neuritis
LL(V)	4	25 (29.7%)	28	5	26
BL(V)	49	19 (38.7%)	15	6	9
BB(V)	24	14 (58.3%)	5	4	1
TOTAL	157	58 (36.9%)	48 (30.5%)	15 (9.5%)	36 (22.9%)
LL(P)	83	23 (27.7%)	24	10	26
BL(P)	41	19 (46.3%)	10	5	7
BB(P)	23	12 (52.1%)	5	2	4
Total	147	54 (36.7%)	39 (26.5%)	17 (11.5%)	37 (25.1%)
		(P = 0.485)	(P = 0.217)	(P = 0.284)	(P = 0.323)

have been segregated into two categories, those having a previous history of neuritis or reactions before commencement of therapy and those without any such history. There were no statistically significant differences in incidence of reactions in patients in the vaccine and placebo groups, adjusting the effect of presence or absence of prior history, in any of the LL, BL or BB leprosy types (Table 4a). The intra-group comparison, however, showed a statistically significant increase in reaction incidence, among patients with previous history, in the placebo group ($P < 0.001$) as compared to those without a prior history of reaction. The similar comparison was not significant statistically in the vaccine group ($P = 0.105$).

Table 4

(a) Impact of previous history of reactions (HOR) on incidence of reactions during MDT and post-RFT follow-up

	Vaccine					Placebo					P*
Group	n	HOR(+)	Incidence	HOR(−)	Incidence	n	HOR(+)	Incidence	HOR(−)	Incidence	V vs P
LL	84	31	23 (74.1%)	53	31 (58.4%)	83	20	19 (95.0%)	63	31 (49.2%)	0.905
BL	49	12	8 (66.6%)	37	16 (43.2%)	41	14	9 (64.2%)	27	8 (29.6%)	0.437
BB	24	7	3 (42.8%)	17	3 (17.6)	23	4	3 (75.0%)	19	6 (31.5%)	0.314
Total	157	50	34 (68.0%)	107	50 (46.7%)	147	38	31 (81.6%)	109	45 (41.2%)	
					P = 0.105$					P < 0.001$	

(b) Impact of previous history of neuritis (HON) on incidence of neuritis during MDT and post-RFT follow-up

	Vaccine					Placebo					P*
Group	N	HON(+)	Incidence	HON(−)	Incidence	N	HON(+)	Incidence	HON(−)	Incidence	V vs P
LL	84	9	9 (100%)	75	22 (29.3%)	83	7	5 (71.4%)	76	31 (40.8%)	0.155
BL	49	8	6 (75.0%)	41	9 (21.9%)	41	3	2 (66.6%)	38	10 (26.3%)	0.929
BB	24	1	1 (100%)	23	4 (17.3%)	23	1	1 (100%)	22	5 (22.7%)	0.085
Total	157	18	16 (88.9%)	139	35 (25.2%)	147	11	8 (72.7%)	136	46 (33.8&)	
					P < 0.001$					P = 0.09$	

P* Intergroup statistical comparison between vaccine and placebo groups, in LL, BL and BB types, adjusting the vaccine effect for the presence or absence of history of reaction/neuritis, done by Mantel–Haenszel chi-square test.

$The intra-group comparison within the vaccine and placebo groups, for incidence of reaction or neuritis, with respect to patients with and without previous history of occurrence.

Similarly, for neuritis, the comparison between the vaccine and placebo groups with respect to neuritis incidence in those with/without a previous history of neuritis did not show any significant difference in any leprosy type (Table 4b). However, a higher incidence of neuritis was found in cases with prior history, as compared to those without such history, within the vaccine group ($P < 0.001$). This difference was not statistically significant in the placebo group ($P = 0.09$).

Table 5 describes the occurrence of neuritis and reactional episodes with respect to the time of occurrence, i.e. whether during MDT or during post-MDT follow-up. It may be noted that in cases of both type 1 and type 2 reactions, majority of episodes occurred during therapy, i.e. 93.0% in vaccine and 93.3% in the placebo group; the rest of the episodes occurred during follow-up. In the case of neuritis, about 18% of episodes occurred during follow-up in vaccine group, as against 9.69% episodes in the placebo group.

Table 6a shows the sex distribution of the patients experiencing the reactional episodes and neuritis. For type 1 reactions, while a nearly equal incidence was observed for males and females in the placebo group (19.5% and 20.8%, respectively), a disparity was observed in the vaccine group patients, where a significantly higher number of male patients developed type 1 reaction in comparison to females (34.5% versus 8.3%, $P < 0.019$). This difference was also found to be statistically significant ($P = 0.02$) when analysed with respect to previous history of occurrence of reaction as shown in Table 6b. For type 2 reactions and neuritis, no statistically significant difference was found in sex distribution, both in vaccine and placebo groups.

Table 7 shows the association of initial BI on the incidence of reaction and neuritis. In vaccine group the reactions occurred in 70.3% cases in high initial (4.1–6.0) BI, 56.1% in medium (2.1–4.0) and 38.8% in low (0.3–2.0) BI patients and this association was found to be statistically significant ($P = 0.0029$). The corresponding figures in the placebo group were also significantly associated with the initial BI ($P = 0.00024$). For neuritis, the frequencies in the vaccine group were 35.3%, 36.3% and 25.9% in the three mentioned BI ranges, while the corresponding figures in placebo group were 43.6%, 39.4% and 21.4%. While borderline statistically significant difference ($P = 0.036$) was observed for neuritis incidence in the three BI ranges, in the placebo group, the difference was not significant ($P = 0.31$) in the vaccine group.

The incidence of impairments such as anaesthesia, trophic ulcers, claw-hand and grade 3 deformities, present before therapy, and those developed during therapy and post-therapy follow-up, were not different statistically in the vaccine and placebo groups. Detailed analysis is reported elsewhere.[7]

Table 5. Incidence of neuritis and reactional episodes, in relation to timing of occurrence during MDT and post-treatment follow-up

	Type 1 reaction (no. of episodes)			Type 2 reaction (no. of episodes)			Neuritis (no. of episodes)		
Group (no. of patients)	Total	During MDT	During follow-up	Total	During MDT	During follow-up	Total	During MDT	During follow-up
Vaccine (157)	72	67 (93.0%)	5 (6.9%)	100	96 (96.0%)	4 (4.0%)	98	80 (81.6%)	18 (18.3%)
Placebo (147)	45	42 (93.3%)	3 (6.7%)	103	100 (97.0%)	3 (3.0%)	105	95 (90.4%)	10 (9.6%)

Table 6
(a) Incidence of reactional episodes and neuritis among males and females

Group (304)	Type 1 reaction (patients affected)			Type 2 reaction (patients affected)			Neuritis (patients affected)		
Vaccine (157)	Total (157)	Male (133)*	Female (24)*	Total (157)	Male (133)	Female (24)	Total (157)	Male (133)	Female (24)
	48 (30.5%)	46 (34.5%)	2 (8.3%)	50 (31.8%)	41 (30.8%)	9 (37.5%)	51 (32.4%)	46 (34.6%)	5 (20.8%)
M vs F, *P* value	$P < 0.019$			$P = 0.683$			$P = 0.277$		
Placebo (147)	Total (147)	Male (123)**	Female (24)**	Total (147)	Male (123)	Female (24)	Total (147)	Male (123)	Female (24)
	29 (19.7%)	24 (19.5%)	5 (20.8%)	51 (34.6%)	41 (33.3%)	10 (41.7%)	54 (36.7%)	43 (35.0%)	11 (45.8%)
M vs F, *P* value	$P = 0.895$			$P = 0.582$			$P = 0.436$		
Statistical comparison between vaccine and placebo groups									
P value		0.010	0.413		0.768	1.00		0.945	0.126

* Previous H/o reactions was present in 44/133 (33.1%) male and 4/24 (16.7%) female patients.
** Previous H/o reactions was present in 28/123 (22.8%) male and 10/24 (41.6%) female patients.

(b) Correlation of type 1 reaction incidence, with previous history of reaction, among males and females

	Males			Females			
Group (304)	Patients with rxn	Patients with HOR(+)	Patients having rxn (HOR+)	Patients with rxn	Patients with HOR(+)	Patients having rxn (HOR+)	*P** (M vs F)
Vaccine (157)	46/133 (34.5%)	44/133 (33.1%)	15/46 (8.3%)	2/24 (8.3%)	4/24 (16.6%)	1/2 (50%)	0.02
Placebo (147)	24/123 (19.5%)	28/123 (22.8%)	9/24 (37.5%)	5/24 (20.8%)	10/24 (41.6%)	1/5 (20%)	NS

* Statistical comparison of type 1 reaction using Mantel–Haenszel test, among males and female patients, adjusted to previous history of reaction.
NS non-significant.

Table 7. Incidence of neuritis and reactional episodes, in relation to initial bacteriological indices

Group	BI range	Total	Reaction		Neuritis		Statistical difference*
			Present	Absent	Present	Absent	
Vaccine (157)	4.1–6.0	37	26 (70.3%)	11	13 (35.3%)	24	
	2.1–4.0	66	37 (56.1%)	29	24 (36.3%)	42	$P = 0.0029$ (Reactions)
	0.3–2.0	54	21 (38.8%)	33	14 (25.9%)	40	$P = 0.31$ (Neuritis)
Placebo (147)	4.1–6.0	39	29 (74.3%)	10	17 (43.6%)	22	
	2.1–4.0	66	33 (50%)	33	26 (39.4%)	40	$P = 0.0024$ (Reactions)
	0.3–2.0	42	14 (33.3%)	28	9 (21.4%)	33	$P = 0.036$ (Neuritis)

*Statistical difference calculated by chi-square for trend test, in the three BI ranges, in the vaccine and placebo groups.

Discussion

Reversal (type 1) reactions (RR) occur frequently in borderline and subpolar LL leprosy but are relatively uncommon in polar LL types, possibly due to the LL patients' inability to mount a CMI response to the pathogen. The occurrence of reversal reaction following immunostimulation has been reported in LL leprosy by Convit *et al.*, where RR was found to be associated with lepromin conversion in indeterminate leprosy patients who were administered multiple injections of a vaccine containing heat killed *M. leprae* and BCG. The reaction was not seen if, either *M. leprae* or BCG were given alone.[8] In another study from Bombay, India, where ICRC vaccine was administered in addition to chemotherapy with DDS, five out of 46 (10.8%) LL patients developed RR.[9] However our findings should be interpreted with caution. The data would have been better analysed using a multivariate analysis. This would have permitted analysis controlling for potentially confounding factors such as history of reaction.

The preliminary results of this trial on RR published earlier (on 106 patients, 53 cases in vaccine and placebo group each) showed an overall incidence of type 1 reaction of 22.6% in vaccine and 15.1% in the placebo group and the difference was not statistically significant.[10] The current study pertains to 304 patients (157 vaccine and 147 placebo cases) who have been followed up for over 8 years where the frequency of RR was significantly higher in the vaccine group as a whole ($P = 0.041$, relative risk 1.79), mainly due to high incidence among LL patients (29.7% in vaccine versus 12% in placebo, $P = 0.009$). This has been found to be due to the higher number of patients in the vaccine group with a previous history of reaction. The corresponding difference was not statistically significant in patients with BL and BB leprosy.

The overall incidence of reversal (type 1) reactions in the present study was higher in comparison to that reported in a few other studies, e.g. 10.8% developed RR following immuno-chemotherapy with dapsone and ICRC vaccine,[7] 8.2% patients in a study from Hyderabad, Southern India[11] and 8–10% occurrence in the study by Chaudhary *et al.* from Calcutta,[12] employing MDT and low-dose Convit vaccine. This disparity could have been influenced by several factors, for example variation in anti-leprosy treatment (dapsone and

rifampicin in study with ICRC and three-drug MDT in other two studies; in fact, no immunomodulator was used in the study from Hyderabad), or a difference in sample size (55, 193, 150 and 304 patients evaluated in studies with ICRC, Hyderabad study, Calcutta study and ours, respectively). In addition, the nature of the study also has a considerable impact on recording of incidence of reactions; the study from Hyderabad was based on retrospective analysis of clinical records of the patients, while other three studies were prospective ones. Ours was an institutional study where all efforts were made to keep the chances of reactions or neuritis going unnoticed, to the minimum.

The incidence of type 2 reactions reported in the preliminary results of our study pertaining to a total of 86 cases from both groups together, was 10/45 (22.2%) in vaccine and 12/41 (29.2%) in the placebo group.[13] The trend observed in the preliminary results is maintained in the data now available, on larger number of patients, followed up for a longer duration. The overall incidence of type 2 reaction was 31.8% in the vaccine and 34.6% in the placebo group (not significantly different statistically).

Recurrence of reactional episodes (single or multiple episodes) has been reported in a study from Thailand where 77.3% patients undergoing type 2 reactions had multiple episodes and 31.4% patients having type 1 reactions had multiple episodes and this difference in occurrence of multiple episodes of type 1 and type 2 reactions was found to be statistically significant ($P < 0.001$).[14] However, we did not find any statistically significant difference between patients experiencing multiple episodes of type 1 (37.5% in vaccine group and 37.9% in placebo) or type 2 (52% in vaccine group and 58.8% in placebo) reactions. There was no significant difference between the vaccine and placebo group patients experiencing multiple episodes of type 1 and type 2 reactions and neuritis.

The occurrence of reactions and neuritis may take place either together or in isolation. In retrospective analysis of reversal reactions in the study from Hyderabad, 19 patients out of 43.1% had skin lesions only, 31.8% only neuritis and 22.7% had both skin lesions and neuritis.[11] The corresponding figures in our study are comparable with these (Table 3). This observation highlights once again the importance of meticulous clinical examination with special efforts to look for inflamed nerves, which otherwise might be overlooked in the absence of inflamed skin lesions.

The disproportionately higher incidence of type 1 reaction noticed among females in the study from Thailand by Scollard *et al.*[14] seems to have been reversed in our study where great preponderance of affected male subjects was noticed (34.5% versus 8.3%, $P = 0.019$) in the vaccine group. One might speculate that this higher incidence in males could be due to the higher number of male patients with a previous history of reactions in comparison to female patients. However, the analysis for the reaction incidence adjusting with the previous history of reaction the statistical difference was done and the difference was statistically significant ($P = 0.02$; Table 6b). The number of female patients in this study as such is very small to draw any concrete conclusion. The corresponding difference was not significant statistically in the placebo group. For type 2 reactions and neuritis, the differences in incidence among males and females were not statistically significant.

The initial BI seems to have a considerable influence on the incidence of reactional states, though the incidence of neuritis does not seem to be affected by it to the similar extent. This is demonstrated by higher frequency of reactions occurring in cases with high initial BI (4.1–6.0), and lower frequencies in the medium (2.1–4.0) and low (0.3–2.0) BI patients (Table 7). Unlike reactions, the statistical difference for neuritis in the different BI categories was non-significant ($P = 0.31$) in the vaccine group and borderline significant ($P = 0.036$) in the

placebo group; the latter does not remain significant on correction applied for the number of variables tested. In our study a great majority of reactional episodes (nearly 93% in both groups) occurred during MDT when the patients were bacteriologically positive. Very few (6–7%) episodes occurred during post-treatment follow-up, when the patients were bacteriologically negative. This could be due to traces (debris) of the mycobacteria, which may not have been cleared completely and could stimulate the immune system. The picture was similar in both vaccine and placebo groups, the plausible explanation could be that MDT was continued in both the groups till the point of slit-skin smear negativity, resulting in marked reduction in incidence of reactional states during follow-up. The incidence of neuritis and reactions was higher in those patients having a previous history of occurrence. This once again stresses the need for more careful monitoring to detect the reactional states and neuritis at the outset among the cases with a previous history of reactions and neuritis.

To conclude, the comparative assessment of incidence of type 2 reaction and neuritis, in the vaccine and placebo group patients, demonstrates no major differences. The incidence of type 1 reaction is higher in the vaccine group in the LL type, but this is also due to significantly higher number of patients having a previous history of occurrence. The more important point to be stressed is that it does not lead to any corresponding rise in impairments or deformity. Therefore it may be inferred that the addition of Mw vaccine to standard MDT does not lead to any appreciable rise in any untoward outcome with respect to neuritis or reactional states, over and above that observed with MDT alone.

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Leprosy elimination at sub-national level

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Summary New strategies for the countries that have already achieved the elimination goal, which includes the great majority of the endemic countries, are needed. There is current concern in these countries about the reduction in the political-technical commitment when the goal is achieved and the possibility of the re-emergence of the disease. A review of the literature on the leprosy post-elimination strategy is done. The proposal to estimate the true prevalence using hidden prevalence based on late diagnosis of the new cases is made. Suggestions are explored for strategies of the work after elimination at national level is attained such as the stratification at the first sub-national level, using estimated true prevalence. It is considered necessary to define strategies for the post-elimination phase with the aim of continuing to the long-term objective of the interruption of transmission and the consequent leprosy eradication.

Introduction

Significant advances have been achieved by the great majority of the leprosy endemic countries towards the objective of leprosy elimination as a public health problem (prevalence rate less than 1 per 10,000 inhabitants) at national level. The countries now need to establish new strategies for the time when they have achieved this objective.

Near the end of 1997,[1] about half (35) of the countries with more than 100 registered cases have achieved a prevalence rate of less than 1 per 10,000 inhabitants at the national level. In another 17 countries (24·6%) the prevalence rate was less than 2 per 10,000 inhabitants and can be expected to attain the goal of elimination in the near future.

The elimination at national level can be considered as the intermediate objective that played an important role in producing a radical change in the work of leprosy control in almost all endemic countries. The political commitment of the governments and funding by governments and by the NGOs (non-governmental organizations) increased. However, this should not be considered the final objective of the work in leprosy. On the other hand, international experience shows that when disease control targets are reached, there is a tendency for activities to decrease. Complacency in considering that the problem has been solved can lead to its return as a re-emergent disease.[2–5]

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This situation has been analysed on many occasions, as in the Hanoi Declaration of 1994,[6] recommending the preparation of the post-elimination phase. Smith[7] emphasizes that leprosy will continue being a problem after the year 2000, and the need for planning the requirements of the next phase. Khalafalla[8] emphasizes the necessity of a strategy by WHO and other relevant agencies to face the problems that will appear after the year 2000, while Lechat[9] indicates that the final objective of leprosy control is the interruption of the transmission. A recent article published by *TDR News*[10] illustrates how '... the success of the elimination strategy leads to thinking, in some areas of the world, that the disease is eradicated'.

At the national technical meeting on the post-elimination stage[11] held in 1993 in Cuba, a country close to achieving elimination, the main actions were established to start programming the activities in this stage. Among the proposals were the following recommendations:

1. To define a 3-year transition step to validate the elimination.
2. To estimate the hidden prevalence on the basis of the proportion of new cases detected late.
3. To prepare a new stratification based on the estimated prevalence.
4. To establish priorities at provincial, municipality, health areas and family doctor sector levels.

At the PAHO-WHO Conference on Leprosy Elimination of the Americas, 1996,[12] the representatives of some countries expressed their concern for the fact that leprosy as a priority had reduced considerably when elimination was achieved, without establishing a strategy for the next stage.

At the Second WHO International Conference on leprosy elimination, held in India,[13] it was established that '... the countries which had achieved the goal of elimination at national level, should focus their attention on the objective of attaining elimination at sub-national level as well as maintaining adequate training and rehabilitation activities. This is important to guarantee that the services are able to assure the continuity in the detection and treatment of new cases, and respond to the medical and social necessities of the individuals affected by the disease. The efforts to assure the elimination of leprosy as a public health problem will establish the basis for leprosy eradication in the future'.

Another aspect that has been emphasized in the literature is the possibility of the existence of a hidden prevalence,[14–16] related to the disease characteristics and the existence of operational problems in the performance of actions in many countries of the world.[16–24] According to WHO data[25] for the year 1997, the hidden prevalence in the world was estimated to be more than 250,000 cases spread in all regions of the world and in the majority of the endemic countries. WHO has proposed to support in the implementation of LEC (Leprosy Elimination Campaign) projects[15] with the objective to identify and begin the treatment with MDT (Multi-Drug Therapy) for the hidden patients.

The aim of elimination as a public health problem is based on the known prevalence or registered prevalence,[14] taking into consideration that it is difficult to know the true prevalence. Despite the efforts made, it is possible that many countries that have achieved elimination have an unknown prevalence. In the post-elimination phase, it is important to consider this situation and try to estimate the true prevalence, thus it is necessary to have methods to estimate this hidden prevalence.[16,19,23,26–28]

It is important to analyse possible strategies for the post-elimination phase, and to develop practical methods of estimating true prevalence using the estimate of the hidden prevalence.

This paper represents a proposal to address this situation by means of elimination at the sub-national level, including methods to approach estimations of leprosy true prevalence through the estimated hidden prevalence.

Estimating real prevalence of leprosy

RATIONALE

It is accepted that the great majority of leprosy patients when diagnosed early do not show evidence of disabilities.[7,16,19,20,24,29–32] The percentage of the cases diagnosed with a grade of disability (including grade 1) can be considered to be a late diagnosis. It is assumed in this proposal that the percentage of new leprosy cases with some disability, among the ones who were evaluated to measure disabilities, can represent an indicator of patients who have not been detected, when applied to the total of new cases detected in the same year.

Assuming an average incubation period of the disease, the sum of the previous 5 years to the year in which we want is used to estimate the hidden prevalence.

It should be taken into account that early diagnosis will be influenced by operational factors (programmes with low performance do not manage to detect cases in the early stages). Therefore with this indicator, the operational component of the problem will be evaluated. Late diagnosis will favour the maintenance of infection sources in the community.

In short, it has been considered that the extent of the leprosy hidden prevalence will be influenced by epidemiological and operational elements, and both of them can be assessed using the percentage of new cases detected with a grade of disability.

METHODOLOGY

The estimated rate of the true prevalence of leprosy is obtained by adding the known or registered prevalence, and the estimated hidden prevalence.

$$\text{Estimated real prevalence} = \text{Registered prevalence} + \text{Hidden prevalence}$$

To estimate the hidden prevalence, we apply the percentage of new patients with any disability (among the ones who were evaluated), to the total of new patients detected. This requires a high proportion of new cases to be accurately assessed. This procedure is used from the previous 5 years to the year we want to estimate. Table 1 summarizes the proposal for collating the necessary information.

When there are interventions to detect the hidden prevalence based on the proposed

Table 1. Chart used to provide estimate of hidden prevalence of leprosy

Indicator/year	19__	19__	19__	19__	19__	Total
a) New cases						
b) Evaluated						
c) Disabled G, 1,2						
d) Percentage of disabled (c/b)%						
e) Estimate of non-detected cases (d × a)/100						

estimation, the evaluation would be related to the number of new cases detected, which should be the same as the sum of estimated hidden prevalence and the usual number of cases detected in the studied area.

Proposal for different strategies at sub-national level

When elimination at national level in a country is achieved, it is necessary to define the possible action scenarios at the first sub-national level (states, provinces, departments), based on the estimation of the true leprosy prevalence. Possible scenarios are that leprosy has not been eliminated, leprosy has been eliminated using MDT, and leprosy was not a problem.

A general strategy should be based on: a) the decentralization of leprosy component actions to the health units at the municipalities (districts); b) the health authorities of the municipality (district) assume responsibility for the management and co-ordination of the actions; and c) the work is done in an integrated way in basic health actions. In large municipalities (districts), defined by geographical area and population size and having many health units, it will also be possible to arrange an internal stratification, giving priority to leprosy actions. For the stratification in this municipality (district) category, it will also be necessary to take into account the possibility of having different health nets (subordinated to the municipality, to other government level, philanthropic or private), in which the patients can be managed or exclusively in one of the nets.

SCENARIO 1: LEPROSY HAS NOT BEEN ELIMINATED.

Implementation and/or strengthening of the Plans of Elimination at the first sub-national level. Health personnel capacity building, strengthening of programme management, and education of the population are still the main actions, with targets of early detection of patients and treatment with MDT/WHO to achieve the cure, to prevent disabilities and to interrupt transmission.

The special interventions such as the WHO projects LEC (Leprosy Elimination Campaign) and SAPEL (Special Action Programme for the Elimination of Leprosy), are still valid based on the existing criteria.

SCENARIO 2: LEPROSY HAS BEEN ELIMINATED BY MDT

Redefinition of the targets

Establishing as a new target a rate of leprosy prevalence less than 1 per 100,000 inhabitants.

Analysis of the transmission trends

Based on new case detection trends, the proportion of multibacillary leprosy and the age average in a period of not less than 10 years, it is possible to make an analysis that allows an estimate of leprosy transmission.

To make this analysis valid, there should be a correlation between the trends and the three indicators, in that when transmission is decreasing, a) a reduction in case detection; b) an increase of the proportion of MB forms, and c) an increase of the age average is

observed. Where this correlation does not exist, it can be considered that the reduction in detection is likely to be a product of operational factors.

Implementation of a net of sentinel centres

Selection of a group of health units spread across the territory can be made to act as leprosy sentinel centres doing negative notification, possibly considering the presence of skin insensitivity as a sentinel event, reporting the number of patients with this symptom resulting in negative leprosy diagnosis.

The capacity of personnel in these health units will be strengthened in suspecting and confirming of the diagnosis, classification of the disease, the administration of MDT, managing reactions and relapses, and the preventing of disabilities.

MDT drug supply

To guarantee MDT drugs supply in small quantities, according to the level of disease prevalence.

Silent areas

In areas where leprosy has been eliminated as a health problem and no new cases are notified, special interventions will be planned in order to confirm if there is interruption in the transmission or if because of operational reasons why cases are not being diagnosed.

SCENARIO 3: LEPROSY WAS NOT A PROBLEM BEFORE MDT

This refers to those areas where no new leprosy cases have been registered in the last 10 years, which can be considered as non-endemic, and in which no special activity is required except routine epidemiological vigilance.

Comments

It is necessary to define strategies to continue the work in leprosy when elimination has been achieved at national level. When this target is reached, a new phase begins with the objective to achieve elimination at the first sub-national level. The objective of achieving the support for the sustained leprosy activities by integration with primary health needs to be based on estimated true prevalence and the different scenarios. The design and implementation of an adequate epidemiological vigilance system of the cases, relapses/reactions and disabilities, needs to keep going until the target of interruption of transmission is achieved.

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A scholarship project for the children of leprosy patients in Turkey

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Summary Most of the leprosy patients in Turkey live in the rural areas of Eastern and South-Eastern Anatolia. Those living in the suburbs of the big cities of the Western parts of the country have come there by immigration. Nearly all patients are very poor; they have no land, or only a small amount of soil for cultivation. The incidence of deformities in our patients is high, excluding them from regular employment and a source of income. In Turkey, it is obligatory to attend primary school, but after that education has to be paid for, and the poor families of leprosy patients find it difficult to continue the education of their children. As the 'Society for the Struggle Against Leprosy', based in the Istanbul Leprosy Hospital at Bakirköy, we have developed a project to enable patients to continue sending their children to school, whilst at the same time asking the mothers to seek advice and guidance on family planning. The outset objective of this project was to enable children and young people, who otherwise have almost no chance of continuing education, to pursue education at secondary, high school and university levels. It was envisaged that in the long term educated children would be able to find a job and provide effective care and support for parents and other members of the family. This paper describes the administrative and other measures adopted and the results of the project from 1995 to 1998, during which a total of 545 children have been supported at an overall cost of US$107,378. The scholarship project has so far been remarkably successful in Turkey and it is hoped that it may provide a model for similar approaches in other countries. An unexpected and extremely encouraging finding has been that females now exceed males in this project and are increasing at all levels, including university entrance.

Introduction

Most leprosy patients in Turkey live in the rural areas of Eastern and South-Eastern Anatolia. Most of those living in the suburbs of big cities in the Western parts have come there by immigration. Nearly all of the leprosy patients are very poor. They have either no soil, or only a small amount of barren soil for cultivation.

In a recent study including 527 male and 184 female patients, the incidences of a) eye

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disorders and b) hand and foot deformities were determined as 75·8 and 73·3%, respectively.[1] Such high rates of disability obviously indicate that patients cannot have a regular job and source of income. Although they are very poor and disabled, nearly all of them, except for those males who are sterile due to erythema nodosum leprosum (ENL), have many children according to the rural traditions. Family planning is not as successful as it should be.

It is hard for the children of poor families living in the rural areas to continue their education after primary school. Boys have few expectations other than being a shepherd or an agricultural worker. Daughters, on the other hand, are taken out of school and forced into marriage when they are believed to have reached 'femininity'.[2] Poor and disabled leprosy patients with many children request social support, particularly money, to maintain themselves, their families and their medical-social care providers.

As the 'Society for the Struggle Against Leprosy', based in Istanbul Leprosy Hospital, we have developed a project to support leprosy patients under the name of the 'Scholarship Project' to encourage them to keep sending their children to school and to have no other children. This is seen as a progressive and positive step, compared to the unconditional allocation of monthly money.

Thus, the family will have a regular income in a project incorporating a strong element of family planning. Those children and youngsters who normally have almost no chance of an education will continue their schools and obtain a relevant job. In the long term, educated youngsters with a job will provide more effective care and support for their poor and disabled parents and the family will at least have an opportunity to escape from the 'poverty trap'.

Materials and methods

In this project, patients who came as outpatients to Istanbul Leprosy Hospital, or who were hospitalized, or examined and controlled at their houses in screening trials or who requested help from our social unit by mail, were evaluated.

Each patient was interviewed personally in the hospital or in their area. When these interviews could not be performed, contact was made by telephone or post.[3]

In the above studies, detailed forms were completed, including the medical and social status of the patient together with the age, gender and educational status of their siblings. Later, the following materials were requested from families and their siblings.

1. Scholarship Requirement Form (from the student).
2. Certificate of Educational Status (from the school).
3. A copy of certificate of birth and a photograph.
4. Bank account number (if under 18 years, of a guardian, if over 18, of the applicant).
5. A certificate indicating that the mother was following some form of family planning (from local government health centre or a government hospital).

As soon as the first five documents were obtained, a financial source for the scholarship was found, or distribution of scholarships began with money obtained from various social activities (teas, meals, fetes/exhibitions and especially the sale of second-hand clothing).

The amount of scholarship money was re-evaluated each year for primary, secondary and high schools and universities according to progress reports and the opportunities available.

Scholarships were sent by bank in two halves, the first being in September for the first 6 months and second in February for the second 6 months of the year.

At the end of each year the students were requested to write a letter to the Scholarship Unit together with photocopies of their school reports. Our main criterion for continued support was the continuation of education, rather than scholastic or academic success and the passing of examinations, taking into account the adverse social and domestic background of many applicants.

To each of the students who sent the school report and the letter, a book suitable for the age and class of the student was sent together with a letter requesting him/her to read and summarize the book in the summer holiday and send it back to us. The letter emphasized the importance and use of education and family planning and of standing on one's own feet by having a job. The same letter procedure was repeated during the postage of the students' money each September. In this way, a direct connection was maintained by correspondence with each student.

Personal files with a photograph, all documents and letters were collected together and maintained throughout the period of support by our scholarship programme. In the following years students were mostly directed towards 'schools of profession'. Very successful ones were sent to preparation courses and when they passed the university examination they were sent to high schools and universities.

When needed, school materials were provided. Those wishing to get a job by doing short-term courses (flower arrangement, hair dressing, modelling, typing, computer etc.) were also supported. Particular effort was given to finding jobs for those who had graduated.

Results

Looking at the distribution of students in our scholarship programme on the map of Turkey, it can be seen that in the top 10 cities, Istanbul comes first and Adana fourth. All the patients in these cities had previously immigrated. All other cities (Van, Elazig, Mus, Malatya, Erzurum, Kahramanmaras, Diyarbakir and Kayseri) are in the Eastern and South-Eastern parts of the country.[4,5]

The scholarship studies were started without having any idea of the likely results and then put on a regular basis. The distributions of students from the last 3 years according to their level of education and gender have been evaluated and are shown in Tables 1–3.

The 445 students shown in Table 2, including 188 females and 257 males, are the relatives of a total of 223 patients. Ninety-two of them had been excluded from the scholarship programme after graduation. Nine of the graduates finished university and 10 students passed university examinations. Eleven students were registered in university preparation courses. In the same year, 1203 books were sent to scholarship students of various years.

Table 1. Scholarships in 1995–1996

Gender	Primary school	Secondary school	High school	University	Total
Female	104	33	36	9	182
Male	108	50	64	24	246
Total	212	83	100	33	428

Table 2. Scholarships in 1996–1997

Gender	Primary school	Secondary school	High school	University	Total
Female	104	32	39	13	188
Male	123	55	60	19	257
Total	227	87	90	32	445

The 545 students shown in Table 3, including 290 females and 255 males, are the relatives of a total of 273 patients.

COSTS

The total cost of this project in the years 1995–1998 comes to approximately US$197,378, taking into account the constantly fluctuating exchange rate.

Discussion

An analysis of the Scholarship Project administered by the Social Unit of Istanbul Leprosy Hospital, Society for the Struggle Against Leprosy, has determined that many negative situations have improved over a period of time.

1. Leprosy patients with the motivation of having a constant income did their best to maintain their children's education and showed care in providing the necessary documents, corresponding regularly and even checking the attendance of their children in school in order to maintain the scholarship, in contrast to a previous lack of interest in the subject of education.
2. Patients who had answered the questions 'Why don't you use methods of family planning; why do you have so many children?' now send certificates of family planning on a regular basis.
3. The decrease in the number of students attending secondary schools and high schools shows that while families still find primary education relevant, they continue to take their children out of school for working in the fields. In the primary school, the number of boys is equal to the number of girls, as it is obligatory to attend primary school. The number of boys attending secondary and high schools and universities increases in the rural areas

Table 3. Scholarships in 1997–1998

Gender	Primary school	Secondary school	High school	University	Total
Female	131	70	67	22	290
Male	130	63	47	15	255
Total	261	133	114	37	545

just as in Turkey in general. However, patients continue to send their children to school without considering any gender difference to get the 'scholarship'.

4. Although a few parents still take their children out of school to work in the fields, this is exceptional. In general, the level of interest in education and attendance rates at school has been excellent. It is particularly encouraging to note (Table 3) that females now exceed males in this project; they are increasing at all levels including university – an unexpected, but extremely encouraging development.

In conclusion the Scholarship Project: a) aims to provide financial support to poor and mostly disabled leprosy patients, b) obliges patients with large families to have no more children and voluntarily to adopt family planning, c) addresses the inequality of gender in education in rural areas, d) proves that the healthy children of a group of patients often excluded from the society can be educated like other people and may excel in their attainments, compared to others living in the same socio-economic conditions, e) encourages leprosy patients to have their children educated, leading to a career, honour and greater confidence and f) improves medical control and therapy by providing close contact between the patient and the health services.

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CASE REPORT

Unusual fixed drug eruption due to rifampicin

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Introduction

Cutaneous reactions due to rifampicin (RFM) are uncommon and amongst these fixed drug eruption (FDE) is especially rare. There have been only three reports of FDE to RFM in the literature so far.[1–3] In 1985, Naik *et al.* first reported a peculiar urticarial type of FDE due to RFM. Here, we describe a second such case with a similar unusual cutaneous drug eruption.

Case report

A 24-year-old soldier suffering from borderline tuberculoid leprosy (BT) was admitted to the Leprosy Center, Base Hospital, Lucknow for supervised institutional therapy. He was put on cap RFM 600 mg once a month and dapsone 100 mg daily. The patient developed a solitary itchy erythematous urticarial lesion of 3.5 cm diameter with typical peau d'orange appearance (Figure 1), on the right side of the chest wall about 1 h after the second monthly dose of RFM. The lesion subsided on its own within 1 h without any residual hyperpigmentation. A similar lesion at the same site was observed following the third monthly dose of RFM which also subsided within 1 h without treatment. At this stage, a clinical diagnosis of FDE was made and all drugs were discontinued. Two days later, the patient was subjected to a provocation test with 600 mg of RFM, following which he developed an urticarial lesion at the same site. The provocation test to dapsone did not evoke any cutaneous reaction. Skin biopsy of the lesion revealed slight dermal oedema and sparse eosinophilic infiltration. Interestingly, this cutaneous response to RFM ceased after the fifth dose of RFM.

In our patient, recurrence of a wheal at exactly the same site following administration of RFM is highly suggestive of FDE. Though FDE can be urticarial, the residual hyperpigmentation that follows a classical FDE was not seen. Moreover, the histopathology was

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Figure 1. Urticarial lesion on right side of chest.

also consistent with urticaria without pigmentory incontinence. The possibility of a type I lepra reaction was not considered, in view of the onset, further evolution of cutaneous eruption and no change in the pre-existing BT lesions.

The outstanding feature of this case is the unusual non-pigmenting FDE to RFM. Moreover, in contrast to the case reported by Naik *et al.*, the urticarial FDE in our case ceased after the fifth dose of RFM. This is probably because sometimes the inducing drug can be readministered without exacerbation and there may be a refractory period after the occurrence of FDE.

To conclude, this case report raises the question whether the urticarial type of FDE due to RFM is truly rare, or is simply under-reported because of its trivial and transient nature. Further studies on this subject may provide an answer.

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Your questions answered

Question:
How should one test for loss of sensation?
Loss of sensation in skin lesions is a sign of leprosy. Sometimes this is marked, but with many leprosy suspects I find myself in doubt about whether it is present. Asking colleagues for their opinion in such cases doesn't always help, as we often come to different conclusions. Have you any advice regarding the procedure for testing for loss of sensation?

Answer:
I think most leprosy workers are familiar with the problem you describe. In my experience, the problem usually lies in making sure the results are interpretable, rather than in the testing technique itself. I can offer the following suggestions.

Be objective in your clinical investigation: for example, favouring a diagnosis of leprosy because you know the suspect has several household members who have (had) the disease, tends to 'influence' your observations.

Be systematic in your approach, i.e. always use the same instruments in the same order and in the same manner. If your procedure includes testing for diminished pain sensation, it is best to do this test last, as the procedure involved may 'blunt' the individual's ability to feel the finer stimuli of instruments testing for anaesthesia to light touch or loss of thermosensation.

First, establish that the individual responds correctly to testing of unaffected skin around the lesion. (Finding diminished sensation in a lesion on the foot of a long-standing diabetes patient does not mean much!) Unless they scores 10 out of 10 with a particular test , it is not useful to then test suspect lesion(s) with that instrument. Many individuals 'improve' their sensation with a little training! One might start out by demonstrating the 'impact' of the instrument on a sensitive area like the face or the back of the hand, before testing the area around the lesion. It may also help to let the subject observe your testing: one often feels better if one sees what one is supposed to feel. You may need to repeat these procedures each time you use another instrument. Remember that people – especially children, anticipating injections – may not feel the instruments because they are afraid of them. Explanations may not always be helpful, and it is often more useful to illustrate the use of the instrument on yourself first.

Now test the lesion itself. Here, it is important to remember that many people want to do well, e.g. because they are eager to please the investigator. Therefore the subject should not see what you are doing. Just asking him or her to close the eyes may not be enough; ask someone to shield the eyes.

Test the lesion and the surrounding skin (or, if the lesion is very big, the corresponding

contralateral area) avoiding any pattern in terms of order or timing: many subjects try to detect a logic to your testing procedure! If blinding of the individual is difficult, such as when the lesion is in the face, and the subject may either 'peep' or detect the movement of your hand, you can test the reliability of the responses by including 'make-believe' stimuli, e.g. bring the instrument to the skin but not actually touch it.

Remember that only part of the lesion may exhibit loss of sensation – sometimes it is a very small part. Thus it is important to test the whole lesion.

If in doubt about your results, you may want to put the patient on observation, and retest the lesions later.

David K. Warndorff
24 Chambrai Close, Appleford, Oxon OX14 4NT, UK

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Teaching Materials and Services

TB Programme Managers Course

The TB Programme Managers Course held in Eithiopia, jointly by the Nuffield Institute, Leeds and ALERT, was evaluated very positively by participants, and the next course will be 16 October to 3 November 2000. The fee is US$2,080 including full board for the 3-week course in Addis Ababa. Contact ALERT@telecom.net.et, or Fax: 00251 1 711199.

Informatics in clinical practice in developing countries: 'still early days'

The following is extracted from a recent issue of the *British Medical Journal* www.bmj.com/cgi/content/full/319/7220/1297:

Tamil Nadu will become the first Indian state to provide telemedicine in the public sector, when a local hospital in the state will be connected to the Chennai Medical College through the integrated subscriber digital network (ISDN) and 'high end' workstations. The state cannot yet connect every district and local hospital to the nearest medical college because the ISDN facility is hardly available outside Chennai. But India has developed technologies for launching missiles and for making nuclear bombs and provides cellular telephones, colour televisions, and luxury cars to the rich. Clearly a case of misplaced priorities. The story is the same everywhere in the developing world.

Consider access to telephones. About 40 countries have less than one telephone for every 100 people. About 25, many in sub-Saharan Africa, have under 0·5 per 100 people. Even India, despite all its scientific and technological credentials and reasonable economic stability, has 1·86 main telephone lines per 100 inhabitants. In contrast, Canada and the United States have more than 60 per 100 inhabitants. The disparity in internet use is even greater.

In addition, most developing countries invest very little in health care. While the world's richest countries spent more than 2500 per capita on health each year during 1990–7, the low income countries hardly spent $15 per capita, just above the estimated $12 a year needed to secure the minimum preventive and essential clinical services. Countries such as Zambia—which spends about $6 per capita on health—and Cameroon, Indonesia, Nigeria, Sri Lanka, and Sudan—which spend less than 2% of gross domestic product—are certainly investing too little in health.

Because of inadequate access to technology and subcritical investments in health care, developing countries cannot to take advantage of technology based advances in healthcare delivery. Besides, medical professionals in these countries are not technologically trained. Even when these technologies are used in the health sector, they usually benefit the urban rich.

To be fair, conscientious doctors have attempted to use informatics to the extent that they could—such as the maintenance of electronic patient records at the Neurosurgery Department of the state owned King Edward Memorial Hospital in Mumbai, India.

Increased use of informatics, can transform health care in the developing countries, but, for now, they have to be satisfied with a few headline grabbing telemedicine projects launched around the world. The International Telecommunications Union has sponsored two conferences on telemedicine for the Third World, one in Portugal (1997) and another in Argentina (1999).

Agencies such as SatelLife and the Midjan Group are trying to make a difference. The HealthNet project of SatelLife uses satellites to connect health professionals in about 30 countries in Africa, Asia, and Latin America. It distributes electronically a weekly newsletter and AIDS Bulletin. The Midjan Group provides European telemedicine services to countries such as Senegal and South Africa. There have also been a few indigenous efforts such as the one in South Korea connecting village medical care centres to the Seoul National University Hospital and Korea University Hospital.

The bottom line is that developing countries, which could benefit most from the use of informatics and telemedicine, have the least access to them. With the right policies, many could quickly marshal the technologies for informatics to improve health care.

Author: Subbiah Arunachalam

International Course on Leprology for Doctors, October 2000 in Valencia, Spain

A recent issue of *Dermatologia y Dermocosmética* carries information about an international course on leprology for doctors (Spanish-speaking) to be held in Valencia later this year. The course is essentially intended for 'Médicos Internos Residentes' in their third year of specialization in dermatology, dermatology specialists, dermatologists in endemic areas of Latin-American countries and other endemic areas, as well as other qualified doctors and specialists with an interest in the subject of leprosy. *Apply* (places are limited) to Dr J Terencio de las Aguas, Tel 609 605 322. Fax 966 42 33 53. E-mail drjoseterencio@hotmail.com.

New website for UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) http://www.who.int/tdr

- Over 500 interactive pages, extensively interlinked, with hyperlinks to key external websites
- Easy-to-use graphical interface, with flexible navigation supported by a full-text search facility
- General information about TDR: strategy, organization, governance, resources and outcomes
- A fully detailed interactive version of TDR's 14th Programme Report 1997–98, with built-in pop-up definition boxes of technical terms
- A complete set of TDR's 'Final Report Series' presenting leading examples of TDR-supported projects
- Full details of TDR grants, workplans, research priorities and deadlines for proposals, with online application forms
- An online database search of over 11,000 research publications arising from TDR-supported research
- Examples to illustrate TDR's trainees, collaborating institutions and partners
- Multimedia resources, including videos and searchable access to the TDR image library—a unique and dynamic catalogue of over 10,000 images
- A complete listing of TDR publications and reports, with recent documents available in portable document format (pdf)
- All the latest news from TDR, including information and articles from TDR's newsletter, *TDRnews*.

Subjects covered: leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, malaria, leprosy, African trypanosomiasis, tuberculosis and dengue.

Research awards in tropical medicine for Young Investigators 2000

Although one deadline (February 2000) has passed, the second (July 2000) may still allow readers of

Leprosy Review to take advantage of the following, or to at least contact the Wellcome Trust for further information and opportunities in 2001.

The Trust encourages young science, medical and veterinary graduates from the UK/Republic of Ireland and abroad to pursue research in tropical medicine by providing opportunities for training and for undertaking research projects in the tropical countries of the world. Studies on all aspects of health and disease in the tropics, including both infectious and non-infectious human diseases in developing countries, are encouraged, together with research relating to veterinary problems in these regions. Cancer and AIDS/HIV-related studies relevant to tropical regions are acceptable.

Research Development Awards

These awards are to enable young clinical (medical or veterinary) and non-clinical researchers from developing countries to establish a programme of research within their home institution with the continued collaboration and support of a UK/Republic of Ireland sponsor. The candidate must have recently completed PhD training or held a research fellowship in the UK or Republic of Ireland. Research proposals should address issues of health and disease that are of regional significance in the country concerned.

All applicants must hold a full-time established post in an appropriate university or research institute in a developing country. Awards are tenable for a maximum period of 3 years. The Trust will provide funds for research and equipment within the applicant's home institution, some assistance towards research costs in the UK/Republic of Ireland and funds for exchange visits.

The closing dates for submission of full applications are 14 February 2000 and 31 July 2000.

Enquiries should be directed to
The Grants Section (Tropical)
The Wellcome Trust
183 Euston Road
London, NW1 2BE
Tel: +44 (0)207 611 8409/8641
Fax: +44 (0)207 611 7288
E-mail: tropical@wellcome.ac.uk

Further details of this and other schemes that may be relevant to individuals, especially medical and veterinary graduates, with an interest in tropical medicine are available upon request from the Trust and can be found at www.wellcome.ac.uk

Asia Pacific Disability Rehabilitation Journal

The latest issue of this journal carries articles on: 25 years of community-based rehabilitation; disability in South-East Asia; training of CBR personnel; rehabilitation and evidence-based health care; integration of disabled people into savings and credit programmes in Bangladesh; integration of disabled people into development programmes—some lessons from OXFAM-GB, Bangladesh. As with previous issues of this valuable publication, this one contains a wide range of information on meetings, training courses and published material on disability. *Editor*: Dr Maya Thomas, J-124 Ushas Apts, 16th Main, 4th Block, Jayanagar, Bangalore 560 011, India. Tel and fax 91-80-6633762. E-mail thomasmaya@hotmail.com.

Publications available free of charge from the Wellcome Trust

These include the following:

Wellcome News

Published four times a year *Wellcome News* examines the progress and implications of the many areas of research funded by the Wellcome Trust. This history of medicine, news about the Trust, and the people behind the research are presented in accessible style and lavish illustration. £: free. Web: Some articles.

LabNotes

Published three times a year, *LabNotes* provides teachers with up-to-date information about research findings in biomedicine and their social and ethical implications. This edition describes genetic modification techniques for animals and plants and discusses in depth the growing controversy surrounding the issue. £: free. Web: PDF. Online resource coming soon.

Annual Record

An annual summary of the Trust's UK and international funding activities; also includes careers funding and success rates, with sections on genetics, the public impact of science, and a brief financial summary. £: free. Web: Full text. PDF of Grants Awarded section.

Wellcome News Supplements

Supplements to *Wellcome News* provide accessible and well-illustrated overviews of important research findings and their historical background. Volume 2 covered Alzheimer's disease, while Volume 3 looked at our current understanding of diabetes and reviewed research being done to produce therapies and offer genuine help for patients. £: free. Web: PDF. Some articles.

Wellcome Trust Review

Published annually and beautifully illustrated. *The Wellcome Trust Review* focuses on major Trust-funded initiatives and research projects in the UK and overseas; the history of medicine; and medicine in society. £: free. Web: PDFs of articles. Short versions of articles.

Copies of Wellcome Trust publications can be requested from: Marketing Department, Wellcome Trust, 183 Euston Rd, London NW1 2BE (Tel: 020 7611 8651; Fax: 020 7611 8545; E-mail: marketing@wellcome.ac.uk). Most publications can also be ordered through the Wellcome Web site (www.wellcome.ac.uk/publications).

Tuberculosis: an Interdisciplinary Perspective

The fact that the World Health Organization has declared tuberculosis a 'global emergency' indicates the serious inadequacy of the ways in which the control methods at our disposal are used. Several books on tuberculosis have been published in recent years, but none have taken a deep and detailed look at the 'holistic' aspects of global tuberculosis control, even though international agencies are increasingly aware of the importance of the numerous factors other than the design and efficacy of therapeutic drug regimens. This unique book fills that gap. Although it deals specifically with tuberculosis, the principles outlined and discussed are relevant to many other areas of global medicine, including the ever-growing problem of HIV/AIDS.

The book, edited by J. D. H. Porter and J. M. Grange, is aimed principally at those involved in the design, establishment and management of disease control programmes at international, national and local levels, and also at a more general readership of epidemiologists, public health officers, community psychologists, and others interested in understanding the human dimension of disease control.

Contents: *Introduction to Tuberculosis and Its Control*: The Global Burden of Tuberculosis (J M Grange); The Politics of Tuberculosis: The Role of Process and Power (G Walt); Public Health and Human Rights: The Ethics of International Public Health Interventions for Tuberculosis (P Pronyk & J Proter); *The Current International Structure*: Tuberculosis in High-Prevalence Countries—Current Control Strategies and Their Technical and Operational Limitations (K Jochem & J Walley); Involving the Private Medical Sector in Tuberculosis Control: Practical Aspects (M Uplekar); *Tuberculosis Treatment from the Patient's Perspective: Social and Economic Dimensions of Treatment-Seeking for Tuberculosis*: The Economics of Tuberculosis Diagnosis and Treatment (S Foster); Socio-Cultural Dimensions in Tuberculosis Control (S Rangan & M Uplekar); Gender Issues in the Detection and Treatment of Tuberculosis (P Hudelson); *Alternative Approaches and Future Directions*: Tuberculosis and Health Sector Reform (E Tayler); Educational Approaches in Tuberculosis Control: Building on the 'Social Paradigm' (T Narayan & R Narayan); and other papers.

Readership: Epidemiologists, public health officers and community psychologists. 528pp 1-86094-143-5 US$68 £36. Published by Imperial College Press and distributed by World Scientific Publishing Co.

Clinical Tuberculosis

This comprehensive and practical book by John Crofton *et al.* on how to diagnose and treat tuberculosis is aimed at non-specialist doctors and other health professionals working in areas with limited facilities. It is written in simple English with a glossary and an index and contains numerous line drawings, diagrams and tables.

The authors have drawn on their extensive international experience, supported by advice from experts in WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) and from experts in Africa, Asia and the Pacific.

Sponsored by IUATLD and TALC (Teaching-aids At Low Cost) more than 75,000 copies of the first edition have been distributed in 16 languages to some 125 countries.

The second edition has been thoroughly revised. With the continued explosion of HIV in association with tuberculosis, that chapter has been completely rewritten and enlarged. The treatment sections have been revised to match the latest recommendations from IUATLD/WHO. This includes an outline of WHO's DOTS (Directly Observed Treatment Shortcourse) Control Programme.

To order the second edition at the special low TALC price of £6.25 per copy including surface mail and £7.25 per copy including airmail, please complete the order form on the reverse side and send it directly to TALC. PO Box 49, St Albans, Herts AL1 5TX, United Kingdom. Tel +44 (0)1727 853869. Fax +44 (0)1727 846852. E-mail talcuk.@btinternet.com

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News and Notes

Mycobacterium bovis: Third International Conference, Cambridge UK, 14–16 August 2000

Following the two very successful International Conferences on *Mycobacterium bovis* held in the Republic of Ireland and New Zealand, it has been decided to hold the third meeting in Great Britain at St. John's College, Cambridge, 14–16 August 2000. This event is being hosted by the Veterinary Laboratories Agency, Weybridge, UK.

The year 2000 is an important time in *Mycobacterium bovis* research with the expected completion of the *M. bovis* Genome Project (funded by the Ministry of Agriculture Fisheries and Food and the Wellcome Trust). It is hoped that this milestone might act as a further catalyst for research into the development of improved vaccines and diagnostic reagents to help in the fight against this important zoonotic disease at the start of the new millennium.

The format of the 3-day conference will comprise:

- Papers by invited speakers
- Selected oral communications
- Selected poster presentations

Seminar topics on the agenda will include:

- disease control
- epidemiology
- modelling disease in domestic animals and wildlife
- molecular typing
- pathogenesis
- immunology
- diagnosis
- mycobacterial genetics and vaccinology

The conference is expected to attract 250 delegates from around the world and an impressive line up of internationally recognized speakers has already agreed to participate.

The conference will be residential, 14 and 15 August but extra accommodation can be arranged at the college for the day before, Sunday 13 August (please specify on reply slip if required).

It is also intended to run a number of workshops following the end of the official conference on 17 August but places will be limited.

Topics will include:

- molecular fingerprinting techniques,
- immunodiagnosis,
- comparative pathology
- vaccine development

Further information:

Conference secretary,
Veterinary Laboratories Agency—Weybridge
New Haw, Addlestone, Surrey KT15 3NB United Kingdom
Telephone 01932 341111 Facsimile 01932 347046
Web site http://www.maff.gov.uk/aboutmaf/agency/vla/vlahome.html

Asian Leprosy Congress, Agra, India, November 2000

The message from the Organizing Committee runs as follows:

Dear Colleagues,

During the 15th International Leprosy Congress held in Beijing in the month of Sep '98 there was a strong desire to hold regional congresses in between the quinquennial international congresses in order to promote more frequent interaction among participants and also to highlight on regional issues, problems and achievements. This desire has culminated in the decision to hold the first Asian Leprosy Congress at Agra, India under the banner of ILA from 9–13 November 2000.

It is only appropriate that the first regional congress takes place in Asia in view of the tremendous problem of leprosy which the continent still is facing inspite of the enormous progress made in combating the disease over the past 10–15 years.

The Congress, apart from discussing technical and research issues, is expected to focus more on the problems of the common leprosy worker in combating the disease and in helping them to find solutions to such problems. This should also help in better interaction between researchers and developers of technical solutions on one hand and the ultimate utilizers of such solutions on the other. In order to promote this approach the organizers of the congress would like to encourage and facilitate participation of as many leprosy workers as possible particularly those involved in leading and organizing the fight against leprosy in the field.

Even though the congress is called Asian Leprosy Congress with focus on Asia, it is expected that the Congress would greatly benefit from experiences in other parts of the world and therefore would welcome participation from everywhere.

On behalf of the Organizing Committee, we extend our cordial invitation to all those interested in the fight against Leprosy to participate in the congress, so that together we can progress towards a world without leprosy which is our ultimate goal.

Chairperson Dr. S. K. NOORDEEN
Organising Committee
Secretary Dr. C. S. WALTER
Organising Committee

GENERAL INFORMATION

Date:
9–13 November 2000

Conference Venue:
Japyee palace, Agra, has been selected as the venue of the congress. Set amidst a sprawling 25 acres of landscaped gardens, water bodies and walk ways, this Hotel is a stone's throw away from the beautiful world famous 'Taj Mahal'.

Congress Language: English

Training Sessions:
Training sessions on various topics will be held in the evenings at the Congress Centre and also at the Central JALMA Institute for Leprosy.

Exhibits:
Exhibitions will be arranged for organizations or institutions wishing to display teaching and learning materials, including books, videotapes, compact disks, foot wears, medical supplies and equipment and other items according to interest of the participants.

Social Events:
Special social events/tours will be organized particularly for accompanying persons. There will also be a reception dinner for Congress participants.

Registration and submission of abstracts of papers:
For information on registration, submission of abstracts and other details please contact at the Secretariat address mentioned below.

Conference Secretariat:
Asian Leprosy Congress
C/o TLM India CNI Bhavan, 16, Pandit Pant Marg
New Delhi-110 001, INDIA
Tel: (91-11) 371-6920, 371-8261, 371-8263, 371-8264
Fax: (91-11) 371-0803, E-mail: tlm india@del2.net.in
Website: www.asianleprosy.com

'Drug resistant TB is spreading worldwide'

This is the title of a report summarised in the *British Medical Journal* of 6 November 1999, page 1220. It reads as follows:

Tuberculosis that is resistant to the standard, four drug regimen has now been found in 104 countries, according to a report released last week in New York.

The report, drawn up by Harvard Medical School and financier George Soros's Open Society Institute, estimates that it may cost up to $1bn (£625m) to fight tuberculosis worldwide.

'We were surprised that multidrug resistant tuberculosis was reported so widely. Nowhere was it going away,' said Dr Paul Farmer, professor of social medicine at Harvard and lead author of the report.

'Hot spots'—areas with high rates of drug resistant tuberculosis—are found in the countries of the former Soviet Union, India, China, the Dominican Republic, and the Ivory Coast.

World Health Organisation (WHO) officials said in the report: 'Tuberculosis control is being neglected in most countries worldwide, and ... MDR-TB [multidrug resistant tuberculosis] is a manifestation of this global neglect.

'It clearly shows the effects on tuberculosis control of the dismantling of public health services, compounded by a generalized socioeconomic crisis in Eastern Europe and the former Soviet Union. In the Russian Federation ... tuberculosis cases have almost tripled in less than 10 years.'

Dr Farmer said: 'This epidemic is only briefly local. It will not remain within borders. Forty two per cent of the Russian problem is in prisons. Prison bars and national borders are inadequate to stop transmission.'

General Vladimir Yalunin, head of the Russian prison service, said: 'About 100,000 people confined within the Russian prison system have been diagnosed with active tuberculosis. About 40,000 of them have multidrug resistant tuberculosis. Every year the penal system of Russia releases 30,000 people into the community with active tuberculosis—about 12 000 of them with multidrug resistant tuberculosis.'

In the report, WHO officials committed the organization to rapidly expanding the treatment strategy

known as DOTS (directly observed therapy, short course) and addressing the emerging threat of multidrug resistant tuberculosis by giving expensive second line drugs to patients with drug resistant tuberculosis.

The Global Impact of Drug-Resistant Tuberculosis, is on the internet at www.soros.org/tb

Global tuberculosis control: three documents from WHO

Dr Paul Nunn, Communicable Diseases Research and Development (including TDR), WHO, Geneva has kindly sent copies of the following:

1. *Prospects for Global Tuberculosis control Under the DOTS Strategy.* WHO/TB/98.251 (English only) by Christopher Dye *et al.* (former) Global Tuberculosis Programme, WHO, Geneva. November 1998. The authors developed 'an age-structured mathematical model to explore the principles of tuberculosis control under DOTS, and to forecast the impact of improved case-finding and cure on TB epidemics in different parts of the world. The *Discussion*, which also summarizes the main conclusions, reads as follows:

A recent appraisal of best buys for research on major microbial diseases concluded that the development of strategies to extend DOTS coverage is one of the highest priorities. The results in this paper back that conclusion by quantifying the large number of cases and deaths that could be prevented by improving case detection and cure rates.

We have shown that the potential impact of DOTS on tuberculosis in many developing countries is even greater than the results achieved in industrialized countries when drugs became widely available 50 years ago. Whereas case detection rates above 70% in Europe during the 1950s were associated with a fall in incidence rate of about 10%/year, it should be possible to generate such rates of decline with lower case detection rates in many developing countries with high TB burdens now. A new DOTS programme will have a bigger impact on incidence if it finds more cases sooner, if efforts are made to treat non-infectious as well as infectious cases, if it replaces a poor programme under which cure rates are low and the incidence rate has been falling slowly (or not at all), and if introduced to a relatively young population. The fraction of deaths prevented will generally be greater than the fraction of cases prevented, the more so if cure rates have been low in the past, and if the new programme treats smear-negative cases. We also find that the fraction of cases preventable by DOTS need not be markedly diminished by a large HIV epidemic. This is true provided case finding and cure rates can be maintained which, of course, is more difficult in an area of high HIV incidence which may have suffered a doubling or tripling of tuberculosis case rates.

The cure rate needs to be high in order to avoid prolonged transmission by those who fail treatment. Although treatment of any quality may reduce the number of TB deaths in the short-term, low cure rates could actually increase the rate of transmission, and hence the number of cases. This re-discovery of Styblo & Bumgarner's result is particularly pertinent now that we have a better appreciation of the worldwide distribution of drug resistant TB. If the principal effect of drug resistance is to reduce the cure rate, further careful calculations are required of the cure rate threshold, below which case finding and treatment will make the tuberculosis epidemic progressively worse.

There are numerous uncertainties in making projections with mathematical models, and their effects are only partly reflected in the bounds of our estimates. Most of what we know about the natural history of tuberculosis—which determines model structure and parameter values—comes from studies in industrialized countries, and yet we are most interested here in the prospects for control in the developing world. Apart from the ranges attached to model parameter values, there are critical but unpredictable external variables. We do not know precisely how many TB cases arise each year, and how many are currently found and cured. Nor can we be sure of the course of the HIV epidemics, which particularly affect projections for Africa and Asia. However, the principles of TB control revealed by our analysis do not depend on the exact results of model calculations. And whilst predictions of the *numbers* of cases and deaths between now and 2020 are subject to great uncertainty, we can be more

confident (roughly to the extent indicated by lower and upper bounds) about comparisons of the preventable *fraction* of the TB burden when control targets are not met by different dates.

Even if WHO targets are met by year 2010, three-quarters of the global TB burden would not be averted over the next 23 years. Better diagnostics, drugs and vaccines, plus targeted preventive therapy, would undoubtedly help. But new control measures with the potential to have a major impact may not be available for years. Meanwhile, the most pressing tasks are to find ways of achieving higher cure rates, and reaching more cases, in the principal endemic countries of the world.

2. *What is DOTS? A Guide to Understanding the WHO-recommended TB Control Strategy Known as DOTS*. WHO/CDS/TB/99.270. Original: English. For the Communicable Diseases Cluster, The International Union Against Tuberculosis and Lung Disease and The Royal Netherlands Tuberculosis Association.1999.

This is a 30 page document, with annexes, describing the DOTS strategy in detail. The *Introduction* reads as follows:

For more than 100 years we have been able to use microscopes to detect the bacterium that causes tuberculosis. For almost 50 years we have had effective anti-TB drugs. Yet, this year, more people will die of TB than in any other year in history. How can this be?

The problem has not been the lack of ways to detect and cure TB patients. The problem has been the lack of organization of services to ensure widespread detection and cure of TB patients, particularly the infectious ones.

Today, however, there is a proven, cost-effective TB treatment strategy known as DOTS. A combination of technical and managerial components, DOTS quickly makes the infectious cases non-infectious and breaks the cycle of transmission. Using DOTS also prevents the development of drug-resistant strains of TB that are often fatal and almost 100 times more expensive to cure.

The strategy has been successful in large and small countries, both rich and poor. Countries achieving high cure and coverage rates include Benin, Guinea, Peru, Nicaragua, China and Viet Nam. In China, cure rates rose from below 50% to more than 95% in areas covered by DOTS, and about half the population of China is covered by the strategy today. In Peru, government commitment for the strategy has resulted in almost 100% DOTS coverage in the country and cure rates of up to 83%.

Several challenges, however, impede the implementation of DOTS. The increasing impact of HIV on the incidence of TB in Sub-Saharan Africa is threatening to overwhelm currently effective TB control programmes. After the collapse of the health care system of the former Soviet republics, TB incidence and mortality are on the rise. Eastern Europe is also seeing a surge in drug-resistant forms of the disease.

Today, the strategy must be adapted to fit specific country situations. For example, in areas of high HIV prevalence, partnerships must be forged between TB and HIV programmes. In Eastern Europe, DOTS must not only be introduced and reinforced, but additional programme elements should be developed to more quickly identify and treat drug-resistant cases.

Since the introduction of the strategy almost 5 years ago, great strides have been made in spreading the message to governments, health care workers and the public about the importance of implementing DOTS. As of 1997, 102 countries had accepted the strategy as policy and had implemented it to varying degrees. However, more must be done to ensure the implementation of DOTS more widely.

This document discusses how DOTS was developed, how it is implemented and sustained, how it differs from other control approaches, and its role within a challenging and changing health care system. This document is designed to give decision-makers with health policy and budget authority a good understanding of the strategy so that they can promote effective TB control in their countries.

2. *The Global Tuberculosis Research Initiative: Research to Make a Difference*
Paul Nunn and Jennifer Linkins, (previous) Global Tuberculosis Programme, WHO, Geneva. WHO/TB/98.248. English only.

The *Executive Summary* reads as follows:

Tuberculosis kills more adults than any other single infectious disease, and the epidemic is

worsening. As an international public health authority the WHO, through its Global Tuberculosis Programme (GTB), has a responsibility to promote the equitable and rational use of the world's TB research resources to achieve the greatest possible health gains in TB control. In 1997, therefore, GTB set in motion a Global Tuberculosis Research Initiative (GTRI) to assess global research needs and identify priorities for reducing the epidemic. The initiative is a consultative exercise involving a broad range of external specialists. This position paper represents GTB's initial contribution to the exercise.

Background to the initiative

GTB set up the Initiative following publication of the report of the WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options. The Ad Hoc Committee showed that funds for the world's health research are often allocated in a non-rational and inequitable manner, with the major health problems of the poor majority attracting only minimal funding. The Ad Hoc Committee recommended an analytic process to help decision-makers to allocate resources rationally. This process consists of measuring the scale of the health problem; understanding why the disease burden persists (for example because of lack of tools or failure to use existing tools efficiently); and agreeing a new research agenda to meet the needs identified, taking account of what is being done already about the problem and how likely the proposed research is to result in a useful outcome. The aim of the GTRI is to begin applying similar logic to the specific problem of TB.

The status of the epidemic

Every year, 7 million to 8 million people develop TB. In contrast to most communicable diseases, the burden of TB is expected to grow in the next 2 decades with the risk that, with no extra effort to control it, there will be 10 million new cases per year by 2020. The spread of HIV-related TB and of multidrug resistant strains of *Mycobacterium tuberculosis* are particular causes for concern.

The impact of TB control efforts today and their potential for slowing the epidemic

WHO's recommended strategy to control TB is known as DOTS: Directly Observed Treatment, Short-Course. This five-point strategy brings together the results of previous decades of work into a practical approach to TB control that represents current international best practice. In studies in Asia and Africa, DOTS has been shown capable of curing 80–90% of patients, and is also highly cost-effective, costing only $1 to $3 per year of life saved in low-income countries. Models developed by GTB suggest that the DOTS strategy has the potential to significantly reduce the size of the TB epidemic: if WHO targets for case detection and cure rates could be met by the year 2000, the global burden of this disease could be cut by more than one-third over the next 2 decades and 32 million deaths could be averted using the DOTS strategy alone.

Why does the disease burden persist?

However, despite the existence of the DOTS strategy, the TB epidemic remains. In line with the Ad Hoc Committee's approach, GTB has made a preliminary analysis of the reasons, as a means of identifying research needs.

Poor use of existing tools. Clearly, a major factor is the failure to use DOTS, the principal existing tool, as widely as possible. Worldwide, DOTS is reaching only a fraction of those who need it. Ninety-four of the WHO's 212 member states have implemented DOTS, and within individual countries, implementation is often uneven. For example, of the total global estimate of TB cases for 1996, only 12% were notified by DOTS programmes. These low coverage rates can be explained largely by the low political priority accorded to TB, and the consequent underfunding of efforts to control it. In addition, certain technical limitations of DOTS, such as the length of the treatment period, may weaken patients' adherence to therapy.

Lack of tools. Another reason for the persistence of TB is the simple lack of more effective tools, such as better drugs and vaccines. DOTS alone cannot prevent the development of TB in those already infected with *Mycobacterium tuberculosis*. Even if the WHO global targets for case detection and cure rates are met by the year 2000, it will take 2–3 decades for incidence to fall to a rate of 2 million people per year.

Lack of knowledge. Finally, some of the burden of TB persists because of a lack of knowledge. For example, the impact of drug resistance on treatment is not fully understood; nor is it clear exactly what constitutes immunity to TB in humans, a factor that may delay the development of a TB vaccine. More knowledge may be needed, therefore, before new or better interventions can be developed.

Research needs identified

From this preliminary analysis, the following research needs are apparent.

- research to widen the implementation of DOTS, using health policy research to understand the current constraints better and, according to what is learnt, operational research to improve delivery;
- the development of new tools to control TB—specifically tools that will be appropriate for the needs of poorer populations;
- research to provide the knowledge base for further or better interventions.

Existing research

The WHO Global TB Programme has set out to determine what research is being done on TB already and whether, and to what extent, this research fits the needs identified above. The Programme conducted a preliminary survey of the major research agencies to determine how much they spent on TB research in 1 year. Using the findings of the survey and drawing also on analyses conducted by the Ad Hoc Committee, the programme found that:

a) global resources for research on tuberculosis are disproportionately small compared to the share of the global disease burden;
b) within existing funds for TB research, the areas of activity that attract most resources are (i) the expansion of the biomedical knowledge base and (ii) the development of certain classes of new biomedical tools; the area that attracts least resources is research to improve existing tools, in the health policy sciences and operational research.

Conclusions

The Global TB Programme concludes that:

1. The TB epidemic is among the world's greatest health problems and is worsening.
2. The DOTS strategy has the potential to reduce the TB burden by more than one-third in 2 decades if properly and rapidly implemented. However, at present only 12% of those who develop TB are being notified by DOTS programmes.
3. According to the preliminary analysis of research needs conducted by GTB, a significant portion of the burden of TB persists because of failure to use DOTs as widely as possible. A further portion of the remaining burden may be attributed to a lack of new tools, and a further portion to a lack of knowledge needed to develop further, or better, tools. This suggests the need for several new research agendas:

    a) research to improve the implementation of DOTS;

b) the development of new tools specifically geared to the needs of low-income countries; and
c) strategic research to provide the knowledge base for further and better interventions.

4. Resources for TB research overall are disproportionately small compared to the burden of the disease. An overall increase in resources will be essential to expand research and development activities to meet the needs identified.
5. Using this position paper as a basis for discussion, the participants in the Global Tuberculosis Research Initiative should discuss and reach agreement on unmet research needs, on the relative priority to be accorded to each of those needs, on the rationale for formulating a new research agenda, and the process for doing so.

New adjuvants for vaccines

The following is extracted from page 4 of *TDR News*, No 58, February 1999:

A variety of novel adjuvants are emerging from research and are currently in clinical trials, with some in clinical use. A new adjuvant licensed recently in Italy (MF-59) with an influenza vaccine was the first to be approved for human use in more than 70 years. Judging by the results of clinical trials, some of the new adjuvants appear to be very promising and capable of significantly boosting the desired immune response. The adjuvants are being used in trials with a variety of vaccines against hepatitis, influenza, cancers and allergies, and also with antiparasite vaccines for malaria and leishmaniasis.

A meeting on novel adjuvants, organized jointly by WHO's Global Programme for Vaccines and Immunization (GPV) and TDR, was held in November 1998 in Annecy, France. Participants at the meeting included some 25 researchers involved in adjuvant research and development in academic institutions and 12 different pharmaceutical and biotech companies. An important aim of the meeting was to help researchers identify which adjuvants are ready to be used in clinical trials, and to strengthen their contacts with companies producing new adjuvants.

All the adjuvants discussed at the meeting are capable of inducing both humoral and/or cellular immune responses, and in mouse models can be shown to bias the immune response towards Th1 or Th2 type immunity. They can be 'active', and modulate the immune response, or 'passive', acting as delivery/depot systems. Studies and trials with a dozen or so adjuvants of different chemical types were reported. Of particular interest to readers of *TDRnews* are trials of new adjuvants with malaria and leishmaniasis vaccines:

- For malaria, an adjuvant consisting of an oil-in-water emulsion—Montanide ISA 720—has proved promising in volunteers with a sporozoite-derived antigen (a synthetic peptide of a surface protein), and is also being tested with different merozoite-derived recombinant antigens in children in endemic areas.
- A saponin-derived adjuvant was used in a trial with the synthetic malaria SPf66 vaccine in Colombia; it produced a better response than when alum was the adjuvant. Saponin-derived adjuvants have been shown in preclinical studies to be capable of inducing long-lasting antibody titres and protective responses with low doses of antigen.
- DNA vaccine trials against malaria in humans—using circumsporozoite antigens—have produced potent CD8 + CTL (cytolytic lymphocyte) responses and many strategies are now being considered to improve the immunogenicity of the vaccines, such as constructing mini-gene DNA vaccines expressing epitopes selected from all genes identified in the *P. falciparum* genome sequencing project.
- For leishmaniasis, candidate subunit vaccines—consisting of several cloned leishmanial antigens, one of which is also a powerful adjuvant—were used to treat drug-resistant mucosal *L. braziliensis* in humans in Brazil. A dramatic improvement was seen in six of the eight patients, suggesting that a therapeutic vaccine may even be able to reverse the pathology associated with this disfiguring disease.

Other types of novel adjuvants in clinical trial include cytokines, e.g. interleukin-12 (IL-12) which plays a central role in protection against intracellular pathogens such as *L. major*, monophosphoryl lipid A derivatives, and non-ionic block co-polymers. Selection of adjuvants for specific use with antigens is, however, still largely empirical and requires a pragmatic approach.

[A full report of the meeting is available from TDR World Health Organisation, 1211 Geneva 27, Switzerland]

Progress in the sequencing of *Mycobacterium leprae*

We are grateful to Dr Stewart Cole, Unité de Génétique Moléculaire Bactérienne, Institut Pasteur, Paris for the following 'Progress report on the project to complete the sequence of *Mycobacterium leprae*—November 1999'.

Background

The *M. leprae* genome sequence project, a high priority for both leprosy research and control programmes, is being undertaken with the financial support of the New York Community Trust (NYCT) and ILEP via the Association Française Raoul Follereau. The work is being directed by the Unité de Génétique Moléculaire Bactérienne at the Institut Pasteur, Paris, and high throughput sequencing and assembly performed by the Pathogen Genome Sequencing Unit of the Sanger Centre, Hinxton.

There have been three distinct phases in the project:

- From 1992–1996, ~1.7 million base pairs (Mb) of genomic sequences were generated by the multiplex sequencing group at Genome Therapeutics Corporation (GTC) and the Institut Pasteur team using the ordered cosmid library generated at the Institut Pasteur as template. About 50 cosmids were fully sequenced.
- In 1997, following the withdrawal of GTC from the project, the Sanger Centre took on the task of completing the genome sequence using a set of 45 cosmids covering the remainder of the chromosome. Funding was generously provided by the NYCT. 38 cosmids, representing a total length of 1.4 Mb were successfully sequenced, fully analysed, then annotated and deposited in the public databases (EMBL/GenBank/DDBJ). As expected of the sequencing strategy employed, there was some overlap between the Sanger Centre sequences and those obtained previously by GTC, and this was useful for the purposes of quality control and error correction. Comparison of the two sets of data revealed an average error rate of 1 per 1674 bp in the sequences generated by GTC, probably as a result of the use of inferior technology. This unacceptably high error rate undermined our confidence in the early sequence data and led us to resequence much of the genome.
- In the fall of 1998, a whole genome shotgun approach was implemented in which DNA from the *M. leprae* strain TN, originally used to construct the cosmids, was nebulized and used to generate a small insert library. Forward and reverse reads were then obtained from ~30,000 clones carrying 1·5–2 kb DNA fragments. A complete assembly of all the data is now available. At present this consists of nine contigs totalling 3338 Mb, and these were assembled from 55,028 reads plus selected cosmid sequences. By changing strategy in this way, we have not only corrected all the errors in the GTC sequence but obtained the missing parts of the *M. leprae* genome as well. The exact size of the genome is not yet known but it is clear that it will be larger than our provisional estimate of 3 Mb. This phase of the project was funded mainly by ILEP but with additional funds to the Institut Pasteur from the NYCT.

The next step

To close the nine remaining gaps, we are currently using primer walking, and combinatorial long-range

PCR reactions to generate templates and sequences. In parallel, a shuttle cosmid library is being screened to identify clones that may span the gaps. It is estimated that the sequence will be contiguous in 6–8 weeks time. A further 2 months will then be required to verify its accuracy and for full analysis and annotation. At this point a publication will be prepared to present the findings and compare the genome organisation with that of the tubercle bacillus.

The future

The genome sequence will not only reveal the genes and proteins of *M. leprae* but also provide us with fresh insight into the genetics, physiology, and biochemistry of the bacillus. The availability of a complete genome sequence for *M. tuberculosis*, and a partial sequence for *M. avium*, enables us to perform in-depth comparisons. It is already apparent that the genetic repertoire of *M. leprae* is much smaller than those of other mycobacteria and that many genes have been destroyed by mutation. This downsizing process may have resulted in the loss of one or more important metabolic pathways and thus imposed a stringent requirement for host-derived growth factors. With the help of bioinformatics, the missing genes and functions can be identified and this will facilitate the conception of new media for cultivating *M. leprae*. Likewise, it is also possible that the missing genes could be replaced by those from *M. tuberculosis* thus generating recombinant forms of *M. leprae*. The ability to grow the leprosy bacillus axenically would greatly facilitate drug development and vaccine research.

Other avenues of clinical importance will benefit from the genome sequence. Knowledge of the genes encoding existing drug targets will allow rapid molecular tests to be developed that are capable of detecting drug resistance without recourse to culture. Such a test already exists for detecting rifampicin-resistant *M. leprae* in clinical specimens and is currently undergoing field-trials. Novel drug targets can also be identified from the genome sequence using bioinformatics and database searches, or through structural and functional genomics. Their essentiality can be confirmed by inactivating the corresponding genes in *M. tuberculosis*.

The small insert clones generated by the shotgun approach will be immensely useful for developing whole genome microarrays that can be used as templates in hybridization experiments. These will enable genetic variability resulting from deletion events to be identified and this, in turn, could serve as the basis of a test to distinguish between different isolates of *M. leprae*. A molecular tool that can discriminate between relapse and reinfection would be of immense value to leprosy control programmes.

AIDS cuts life expectancy in sub-Saharan Africa by a quarter

The spread of HIV and AIDS in sub-Saharan Africa has far exceeded the worst projections, according to speakers at the 11th international conference on AIDS and sexually transmitted diseases in Africa. In 13 countries the prevalence of HIV infection is more than 10%, and in some it is as high as 30%. At the conference in Lusaka, Zambia, last week, the epidemic was described as an unprecedented threat to the region's economic development.

At the end of 1998, 22.5 million people out of the region's population of 600 million were living with HIV or AIDS; this number includes 1 million children. The epidemic in sub-Saharan Africa accounts for two-thirds of the worldwide total of 34 million people with HIV/AIDS. About 7500 people are infected daily.

In only two countries, Uganda and Senegal, does the epidemic seem to be abating. Strong governmental leadership in these countries ensures that there is universal health education, that condoms are easily available, and that there is coordinated action from the government.

Life expectancy in the region has decreased from 64 to 47 years. Sixty-five per cent of patients in medical wards in Zambia, and 75% in paediatric wards, are infected with HIV or have AIDS, and the underfunded health system is near to collapse. Even common drugs such as co-trimoxazole are scarce.

In Zambia, a 15 year old has a 60% chance of dying of AIDS. As the epidemic, which is driven largely by poverty, continues to grow, there is little sign of wide-spread change in sexual behaviour, especially among teenagers, one of the most vulnerable groups.

Tsepo Sitali, aged 8, described to the conference the anguish of her friend who will mark her eighth birthday without a mother or a father because both died from AIDS last year.

Tsepo's friend is not alone: the number of children orphaned by AIDS in Zambia is forecast to reach 500 000 by the year 2010. The epidemic affects children not only directly through infection being spread from mother to child but also through the deaths of their parents which results in their being forced into prostitution and other forms of exploitation.

Children, especially girls, are taken out of school to nurse sick relatives or because school fees are no longer affordable. Only an estimated 10% of the predicted illness and death has occurred: the full impact on people, communities, and economies is still to come.

Source: *British Medical Journal* 25 September 1999 page 806.

UN warns that AIDS deaths are set to reach record level

A record number of people will die from AIDS this year despite the improvement in survival achieved with antiretroviral therapies in wealthier countries, a report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) warned this week.

UNAIDS estimated that 2.6 million people will die from diseases related to HIV and AIDS during 1999—a higher global total than in any year since the beginning of the epidemic. With the HIV positive population still expanding—there were 5.6 million new infections during this year alone—the annual number of deaths was expected to continue to increase for many years.

The report estimated that 32·4 million adults and 1·2 million children would be living with HIV infection by the end of 1999. About 95% of those infected live in the developing world, and this proportion was predicted to rise even further as infection rates continued to rise in countries where poverty, poor health systems, and limited resources for prevention and care fuelled the spread of the virus.

Sub-Saharan Africa continues to bear the brunt of HIV and AIDS, with close to 70% of the global total of HIV-positive people. Most will die in the next 10 years, joining the 13·7 million Africans already claimed by the epidemic. Figures suggest that 55% of infected adults in Sub-Saharan Africa are women. UNAIDS director Dr Peter Piot said: 'Today we see the evidence of the terrible burden women now carry in the African epidemic.'

UNAIDS pointed out that HIV also remains a challenge in industrialized countries. Dr Piot said: 'There is evidence that safe sexual behaviour is being eroded among gay men in some western countries, perhaps because of complacency now that life-prolonging therapy is available.' If this was the case, the report warned that the complacency was misplaced: 'The disease remains fatal, and information from North America and Europe suggests that the decline in number of deaths due to antiretroviral therapy is tapering off.'

The report added that HIV infections in the former Soviet Union have doubled in just 2 years, and that injecting drug use gave eastern Europe and Central Asia the world's steepest increase in HIV infection in 1999. Half of all people infected with the virus were infected before they reached the age of 25 and typically died by 35.

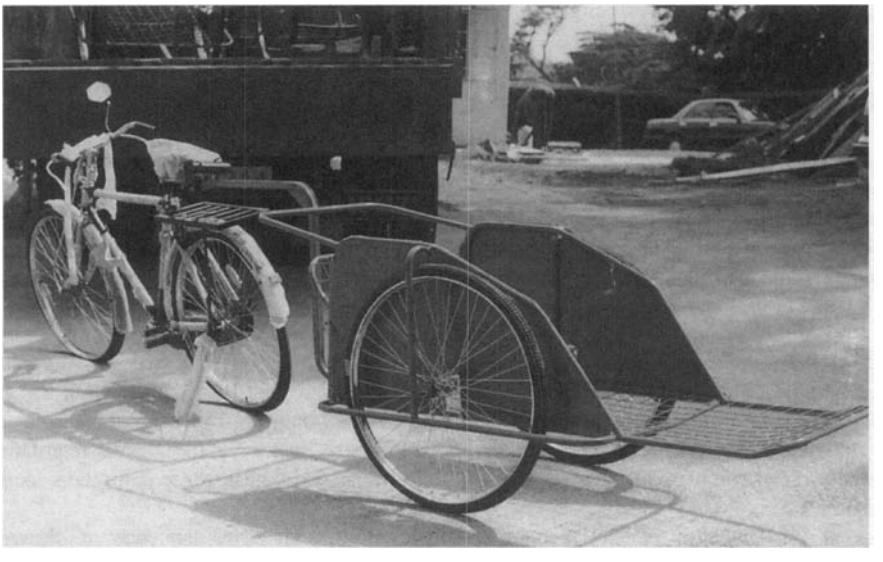
AIDS Epidemic Update: December 1999 is available free from UNAIDS, 20 Avenue Appia, 1211 Geneva 27, Switzerland, or on the internet at http:www.unaids.org

Source: *British Medical Journal* 27 November 1999 page 1387.

A 'bicycle ambulance' from Uganda

A previous issue of *World Health*, 51st year, No 1, January–February 1998 carried the following information:

One of Uganda's responses to the problem is the introduction of the 'bicycle ambulance'. Designed for both flat and hilly areas, health workers in several districts are now trying out this practical vehicle, sponsored by the Ministry of Health, UNICEF and WHO. It consists of an ordinary bicycle with a specially designed trailer attached to it in which health workers can transport a pregnant woman or sick patient. On rugged or smaller village paths or up hills, it may be necessary for more than one person to help pull the trailer. In such situations, it can easily be detached from the bicycle. Maintenance and running costs are small and affordable for most communities. Following an evaluation of the bicycle ambulance, it is expected that the scheme will be extended to other districts in Uganda.



Further information is available from Dr A K Mbonye, Principal Medical Officer, Reproductive Health, Ministry of Health, PO Box 7272, Kampala, Uganda.

The myth of the spread of leprosy with the Crusades

The following is the summary of a paper presented by P D Mitchell, Wellcome Institute for the History of Medicine, University of London, 183 Euston Road, London NW1 2BE, United Kingdom, at a meeting in Bradford (UK) in July 1999 on 'Past & Present of Leprosy':

Many authors have proposed that returning crusaders in the 12th and 13th centuries were responsible for the apparent dramatic rise in the prevalence of leprosy in mediaeval Europe. In support of this view, the European written texts mention leprosy little before this time and leprosaria were scarce but from the 12th century onwards leprosy was the focus of significant sections of medical manuscripts and hundreds of leprosaria were built. However, a more critical assessment raises serious doubts about the interpretation of this evidence. The epidemiology is not suggestive of an epidemic. When leprosy is introduced into an area for the first time and an epidemic occurs, the vast majority of cases are tuberculoid while only a few are lepromatous. In contrast, excavation of 12th century leprosaria in Europe show mostly lepromatous and few tuberculoid cases. While it is not

known what proportion of actual lepromatous and tuberculoid cases were identified and segregated at that time, it can be said that these findings do not support an epidemic theory. Furthermore, it is known that leprosy was present in Europe 500 years before the crusades and any epidemic should have happened then.

While it is true that the number of leprosaria greatly increased at the time of the crusades, the number of general hospitals did too. This suggests a change in social attitudes to caring for the sick, rather than more leprosy patients. The larger sections on the disease in medical texts may have been a consequence of the extra information available from the translation of Arabic manuscripts at that time. In any case, to implement the laws requiring segregation of patients doctors needed good knowledge of the symptoms of leprosy to minimise incorrect diagnosis.

There is little evidence to blame the crusades for a leprosy epidemic. Any true increase in prevalence might be better ascribed to increasing population density and urbanization.

First human chromosome (22) sequenced

Wellcome News (Research & Funding News from the Wellcome Trust, London, UK), Issue 21, Q4, 1999 carries the following:

Researchers from the Sanger Centre near Cambridge, Keio University in Japan and US laboratories at the University of Oklahoma and Washington University, St Louis, have published the complete sequence of human chromosome 22—the first human chromosome to be fully sequenced. The sequence was published in the 2 December issue of *Nature*.

Chromosome 22 comprises 34 million nucleotides, and appears to encode at least 679 genes, of which 55% were previously unknown in humans. The work provides insight into the way genes are arranged along a strand of DNA, and how they might be controlled. Previous research has already revealed that genes on chromosome 22 are implicated in the function of the immune system, and in several inherited conditions, including congenital heart disease, schizophrenia, mental retardation and some cancers. The complete sequence will greatly aid research on these genes and others located on chromosome 22.

Mike Dexter, Director of the Wellcome Trust, commented: 'The sequence of chromosome 22 includes 298 genes previously unknown in humans, which are being released without the constraints of patents and fees. The fact that all of this information is now freely available for scientists to use is of major importance, if the knowledge of our genetic make-up is to be used for the good of humankind.'

A first draft of the full human genome is still scheduled for early 2000. In November, the international Human Genome Project consortium celebrated depositing one billion base pairs of DNA sequence in the public databases—effectively one-third of the entire human genome.'

The summary of the *Nature* publication referred to above (*Nature*, 402, December 1999, 489–495) reads:

'Knowledge of the complete genomic DNA sequence of an organism allows a systematic approach to defining its genetic components. The genomic sequence provides access to the complete structures of all genes, including those without known function, their control elements, and, by inference, the proteins they encode, as well as all other biologically important sequences. Furthermore, the sequence is a rich and permanent source of information for the design of further biological studies of the organism and for the study of evolution through cross-species sequence comparison. The power of this approach has been amply demonstrated by the determination of the sequences of a number of microbial and model organisms. The next step is to obtain the complete sequence of the entire human genome. Here we report the sequence of the euchromatic part of human chromosome 22. The sequence obtained consists of 12 contiguous segments spanning 33·4 megabases, contains at least 545 genes and 134 pseudogenes, and provides the first view of the complex chromosomal landscapes that will be found in the rest of the genome.'

'American Experience With Low-Dose Thalidomide Therapy for Severe Cutaneous Lupus Erythematosus'

The following is a summary of an article recently published in *Arch Dermatol*, 1999;**135:**1079–1087:

Background: There is a renewed interest in thalidomide therapy after its surprising effectiveness in treating erythema nodosum leprosum was first published. Thalidomide has subsequently been reported to be effective in treating a number of dermatoses, including cutaneous lupus erythematosus. We examined the efficacy and adverse effects of low-dose, long-term thalidomide monotherapy in seven patients with various forms of cutaneous lupus erythematosus that were unresponsive to traditional systemic treatments.

Observations: Six of the seven patients treated with thalidomide after discontinuation of other oral agents had complete or marked resolution of their previously treatment-resistant cutaneous lesions, with an average response time of 2·2 ± 0·8 months. Our cohort of seven patients with cutaneous lupus erythematosus was treated with thalidomide therapy for an average of 2·4 ± 3·1 years (range, 1 month to 9 years). The most common adverse effects were sedation, constipation, and weight gain. Two patients reported experiencing intermittent shaking episodes, an adverse effect not previously reported in the literature. Four patients reported symptoms of paresthesia, but none was found to be caused by thalidomide-induced peripheral neuropathy.

Conclusions: A low starting dose of thalidomide as a monotherapy with continued sun avoidance is a safe and effective treatment for the various cutaneous manifestations of lupus erythematosus after traditional therapeutic options have failed to control disease. Our experience with low-dose, long-term thalidomide therapy suggests that peripheral neuropathy is not as common as suggested by other studies (up to 50% of patients treated with thalidomide in some series).

Zinc deficiency; association with reduced immuno-competence and increased rates of serious infectious diseases

Over a period of several decades, the leprosy literature contains articles on the possible importance of zinc deficiency, many of them including reference to its importance in the healing of chronic ulcers. The authors may be interested to know of an article recently published in the *Journal of Pediatrics* 1999; **135:**680–697 in the context of prevention of diarrhoea and pneumonia. Extracts from the commentary published in the *British Medical Journal* of 11th December 1999, page 1521, read as follows:

Zinc deficiency is common in young children in the developing world and is associated with reduced immunocompetence and increased rates of serious infectious diseases. Several trials in poor countries have shown the benefit of zinc supplementation in reducing infection (*BMJ* 1998;**317:**369), but these have varied in the magnitude of the effect and the presence of a differential effect by age and sex. Some trials were underpowered to detect the effects on infrequent outcomes, and others remain unpublished.

A pooled analysis was conducted by the Child Health Research Project, a group of researchers from Johns Hopkins School of Public Health and the World Health Organisation, who had access to the original trial data. Trials were included if they provided oral supplements containing at least half the US recommended daily allowance of zinc for children, and if morbidity surveillance was carried out for at least 4 weeks. Two sets of trials were identified—those in which zinc was given continuously, and those giving only a short course.

For the zinc supplemented children in the seven continuous trials, the pooled odds ratios for diarrhoeal incidence and prevalence were 0·82 (95% CI 0·72 to 0·93) and 0·75 (0·63 to 0·88) respectively. Supplemented children had an odds ratio of 0·59 (0·41 to 0·83) for incidence of pneumonia.

No significant variations in the effects were seen in the subgroups of children stratified by age, sex, and weight, and nor was there a significant difference between short course and long term supplementation.

The authors conclude that 'the development of effective and feasible interventions to improve the zinc status of developing country populations is essential.' One such intervention, zinc fortification of bread, was shown in a randomised controlled trial to reduce diarrhoea, respiratory illnesses, and skin infections in Turkish schoolchildren (*Cereal Chemistry* 1995;**73:**424–426).

Dr Robert Black, of Johns Hopkins School of Public Health and co-author of the study, said: 'Zinc fortification is potentially a powerful tool for settings which produce commercial food, and the idea has been acceptable to food manufacturers. If there's no commercial food, increasing zinc intake is possible by reducing the amount of dietary phytates, which interfere with zinc absorption. This can be done by soaking or fermenting food. Long term, it is possible that plant breeding could be used to increase zinc or reduce phytate content.'

But several questions still remain before zinc therapy can be incorporated into diarrhoeal disease control programmes, including the optimal dosing regime and duration of therapy. Dr Shammim Qazi, from the Division of Child Health and Development of the World Health Organisation, said: 'At present the WHO is not recommending zinc supplementation as routine. We are waiting for the results of larger trials, and we are planning a trial ourselves.'

[The Child Health Research Project's Special Report '*Zinc for Child Health*' is at http://ihjhsph.edu/chr/publicat.htm. An excellent account of zinc deficiency is to be found in Dermatology in General Medicine, 4th edition, 1993, Chapter 146, pp 1826–32].

Second round of modified leprosy elimination campaign (LEC) in the State of Orissa, India, yields fewer cases

A report in the *Indian Express* on 8th March 2000 suggests that the incidence of leprosy in Orissa, based on recent findings in a second LEC, is declining. In a recent press release, the Assistant State Leprosy Officer, Dr PKB Patnaik, reported that 27,197 cases of leprosy were detected during the second LEC, compared with 62,844 during the first—an apparent fall of 57% in 2 years. The second LEC took place between January 30th and February 4th, 1999. Search teams of male and female workers visited each family, with the help of one volunteer for every 600–900 of the population. About 1225 mobile conformation teams, consisting of one medical officer and one paramedical worker (leprosy) examined the 185,548 suspects identified. Eighty-five percent of the population was contacted during the campaign.

TB Alert/TB Focus, London, UK

A meeting of TB Alert in London on 22nd March, 2000 included the announcement of a 'sister' organization called TB Focus, intended to concentrate on medical research and scientific work in TB. Further details and description of projects to be undertaken will be reported at a later date.

The meeting was held in the Post-Graduate Centre of the National Heart and Lung Institute, Brompton Hospital, London and included presentations on the management of TB patients in London; vitamin D deficiency and vitamin D receptor polymorphisms as risk factors for TB among Gujarati Indians (in the London area); TB in the United Kingdom; the *Mycobacterium tuberculosis* genome; problems in TB control in the UK. TB Alert, as previously described in this journal, continues to campaign for better awareness of the TB problem, both in the UK and worldwide, whilst bringing together people in the UK with a common interest in the subject of TB, and the global emergency.

Further information: Paul Summerfield, 22 Tiverton Road, London NW10 3HL United Kingdom Tel: 0181 969 4830 (from outside UK +44 181 969 4830) Fax: 0181 960 0069 (from outside UK +44 181 960 0069) E-mail: tbalert@somhealy.demon.co.uk

Mini Leprosy Guide and NLO Diary 2000

The National Leprosy Association, India has announced the release of their Mini Leprosy Guide and NLO Diary 2000. The Diary is printed in English, Marathi and Hindi. In addition to a calendar and address book, it contains useful information on the diagnosis and treatment of leprosy, MDT coverage in India, case detection and books and journals on leprosy. The price of the Diary is Rs.25/- in India and postage is US$3.00 outside India. Payment is through a banker's draft on any branch of the Bank of Bhilai (cheques not acceptable), made out to 'National Leprosy Organisation, India'. For further information, please contact: National Leprosy Organisation, India, Dhour, Durg, 450 024, India.

IDEA Newsletter

The following extracts are taken from IDEA's Newsletter of March 2000:
'Dear Friends
This Saturday is March 11, the Second Annual International Day of Dignity and Respect. Last year, this day was commemorated at Carville, and also in different ways in China and India.

In reality, every day is a day of dignity and respect as far as IDEA is concerned. But it is also worthwhile to continue to observe this, and encourage others to do the same. This is not to be in competition with World Leprosy Day but something completely different – a day when we think about dignity and respect, rather than focusing on the physical aspect of the disease, treatment, etc.

We are in the process of putting together a book of quotations called *Freeing Ourselves of Prejudice. Thoughts on Dignity, Disability and Discrimination.* We will publish this in many languages. It will not be a thick book but will be something we can use to share words and ideas and thoughts of people around the world with others who have also had the disease. We thing that this will be an important empowerment tool as well as provid(ing) us all with a means of sharing the word of IDEA members with others.

Therefore, as this year's International Day of Dignity and Respect approaches, it would be helpful if you would spend a little time thinking about dignity and respect, and send me your thoughts you have that can be included in this book or other educational materials. We will publish this book in commemoration of the Second International Day of Dignity and Respect.

Also, and this is very important, at the end of the new Quest of Dignity Exhibit we will have a panel that says 'The Quest for Dignity is not over. It has just begun.' (This panel will be) translated into many languages. This quote was originally from Therea Wilson from Carville. So, I need your help to translate this quote into your local language.

Despite the fact that the situation at Carville has changed quite a lot since last March 11, everyone who participated in the First International Day of Dignity and Respect at Carville felt this was so important. It was an opportunity to voice their feelings rather than just passively accept the decisions of the administration and health officials in Washington.

. . . . . we are updating and really changing the Quest for Dignity Exhibit. In the last 2 years, we have received so many new quotes and photos that we now have the voices of 70 different people who had HD from more than 20 countries as part of the exhibit and photos from 28 different countries. The Exhibit is now much more lightweight and easier to transport and also doesn't require a lot of labour to put up. So, it will be able to travel to more places. we are also producing a French version and Italian version. The Nippon Foundation has again provided us funding for the Exhibit. The new Exhibit will be launched in Luxembourg in mid-April.

In conclusion, some words form Bacurau, which are very appropriate for the Second International Day of Dignity and Respect:

'We will no longer bow our heads. We'll hold them high. By our strength of purpose we will no longer feel ashamed or guilty. We will no longer have the fear of rejection. Most important, we will not be denied our human rights. We will maintain our esteem and dignity . . . . . There is no turning back.'

Portraying a positive image of persons (previously) affected by leprosy

The following article, by Wim Van Brakel and P. K. Gopal, was recently published in the *International Journal of Leprosy* and as a communication in *ILEP Flash.*

In the March 1999 issue of *Leprosy Review*, the report of Workshop I on 'Social aspects and rehabilitation', held during the 15th International Leprosy Congress in Beijing, was published.[1] Recommendation 1 (page 86) reads: 'Guidelines for appropriate terminology, taking into consideration cultural differences, should be developed with input from people affected by leprosy. These guidelines should be published and distributed.'

The text below has been adapted from an article published in the *ILEP Flash* last year. While it does not present comprehensive guidelines on the subject of terminology mentioned above, we would like to offer it as a contribution towards the development of such guidelines.

In recent years, many have come to realize the important role of language and terminology in social stigma against people with many chronic conditions.[2–5] People with impairments or disabilities were labelled for life as the 'disabled' or the 'handicapped'. People who were suffering from AIDS were called 'AIDS patients' until their death.[6] Strong appeals, particularly from the affected people themselves, have led to changes in terminology.[7] The 'disabled' are now called 'people with disability' or 'differently abled people'. The blind and deaf, in a dignified way, are called 'visually handicapped' and 'hearing impaired', respectively. Instead of speaking of 'AIDS patients', many publications now talk about 'people with AIDS'.

In the field of leprosy, the situation has been very similar. It is possible that the social stigma against people affected by leprosy has been even stronger than against people suffering from other chronic conditions. The word 'leper' has become almost synonymous with 'outcast'.[2,8,9] In a quest to restore dignity to those who have had leprosy, the affected people themselves, as well as many leprosy workers, have started to call for a change in the language used in the field of leprosy.[1] Particularly instrumental in this is the organisation 'IDEA', the International Association for Integration, Dignity and Economic Advancement. During the 2nd International Conference on the Elimination of Leprosy, a major discussion was held on this topic. Dignity and the use of positive language to promote dignity was also a subject of discussion during the Workshop on People Affected by Leprosy as Working Partners during the 15th International Leprosy Congress in Beijing. Many people who themselves had been affected by leprosy were present at both events.

There is a strong feeling that if someone who has (had) leprosy is always being labelled as a 'leprosy patient' or even just as a 'patient', this will have negative consequences for that person. Given the social stigma against leprosy, this label wrongly gives the impression that an affected person will always remain a patient, and thus is never cured. From a rehabilitation point of view, it would be very desirable to change positively the terminology used in this field. The attitude conveyed by the behaviour of the health worker towards patients as also very important in this context.

To promote the use of positive terminology in relation to people affected by leprosy, we would like to make the following recommendations:

1. The use of the word 'patient' should be context-dependant. It is only appropriate in a medical context of a health worker–patient relationship.
2. The preferred term to use when referring to an affected person, when his/her association with leprosy needs mentioning, is a 'person affected by leprosy (or Hansen's disease)'.
3. In situations when the relation with leprosy is irrelevant, e.g. in many rehabilitation situations, a description such as 'person with disability', or simply 'person' or 'affected person' would be preferable.

4. Recommendations for a change of terminology should be prepared for a wide range of uses, including the media, health training materials, legal documents and medical/technical papers and publications. Manuscripts and other media materials should be reviewed with regard to terminology, where possible by people affected by leprosy themselves.
5. The importance of health workers acting out a positive attitude toward leprosy patients should be emphasized whenever possible. Training to this extent should be included in leprosy courses, particularly those for general health workers.

It is encouraging to see that in several organizations, the term 'person affected by leprosy' has been readily accepted. However, unfortunately, people have started abbreviating this term to 'PAL'. They have now started speaking about 'pals' when referring to people affected by leprosy. This practice is undesirable for two reasons.

First, the word 'pal' is a very colloquial word for 'friend', while it is often used in situations where the use of the word 'friend(s)' would be inappropriate.

The second is the major reason for not using the abbreviation 'pal'. The use of a special word like 'pal' is essentially the same as using the word 'leper'. The use of a special term will label people as different from other people, which is exactly what we want to avoid! We don't do around or write about people with tuberculosis or malaria as 'pals', so why should we do this to people affected by leprosy?

What we try to achieve is that the language and terminology used to describe people who have (had) leprosy is as normalized as possible. If we abbreviate 'person affected by leprosy' to 'pal', we will be using this word all the time. If we use the 'full form', we can be flexible: one time talking about 'the affected person', another time 'the leprosy-affected person', or just 'the person'.

We would therefore like to make a strong appeal to anyone working in the field of leprosy, or anyone otherwise needing to talk or write about leprosy-affected people: for the sake of dignity of the persons affected by leprosy, please do *not* use the word 'pal'!

It is also important to realize that English is not the main language in most leprosy-endemic countries. Rotburg highlighted differences in stigma attached to the word 'leprosy' in South America and Europe.[2] Jeanette Hyland made a strong plea for researching the best word or label in different cultural contexts.[9] It is therefore essential to initiate a discussion in all endemic countries about non-stigmatizing terms that would be appropriate in the different languages spoken. In Nepal, this discussion has led to agreement to use the term 'kustha prabhabit byekti' as the Nepali equivalent for 'person affected by leprosy'.

We hope that our concerned efforts at introducing and using positive language in relation to people affected by leprosy will help to rase their dignity and will slowly push back the age-old stigma attached to the disease!

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Erratum

In the December 1999 Special Issue of *Leprosy Review*, the article entitled 'Leprosy elimination campaign (LEC) in Myanmar, 1997 to May 1999' was erroneously attributed to T. Shwe. The author of this article is Dr Kyaw Nyunt Sein, National Programme Manager, Department of Health, Myanmar. We apologise for this error, and for any confusion that may have arisen.

Instructions to Authors

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